



6541620

Inventor: Brewer et al.
SN 08/484,337
Title: Tumor Necrosis Factor (TNF)
Inhibitor and Method for Obtaining Same
Application/Docket: 99,369
Group Art Unit: 1647

FIG. 1

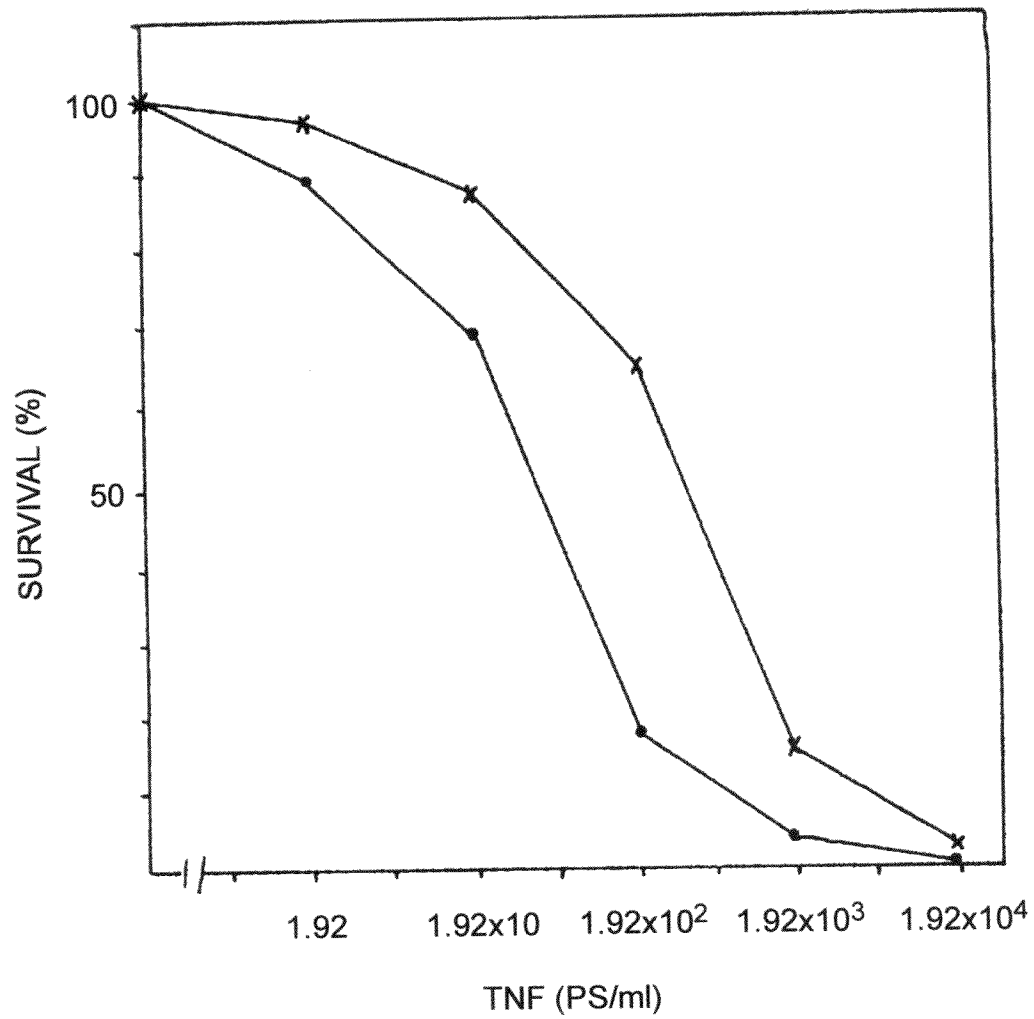


FIG. 2

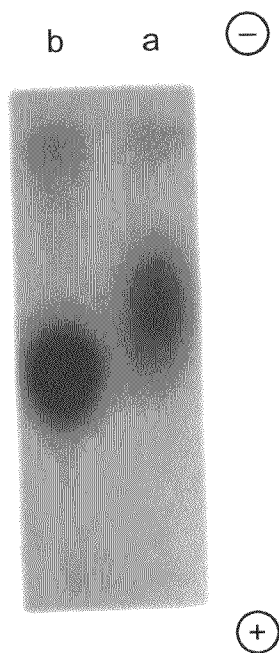


FIG. 3

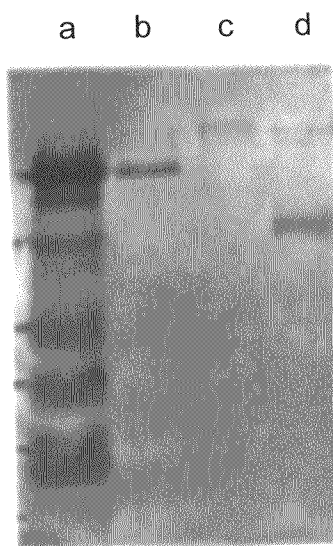


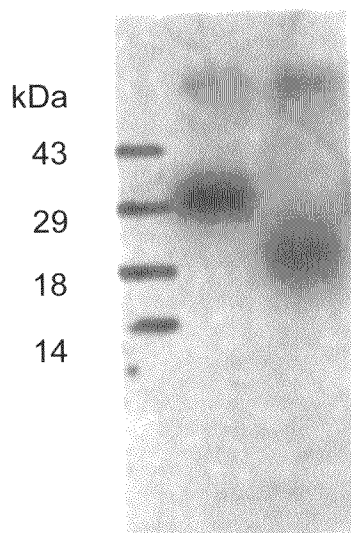
FIG. 4

a b c d



FIG. 5

a b





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FIG. 6A

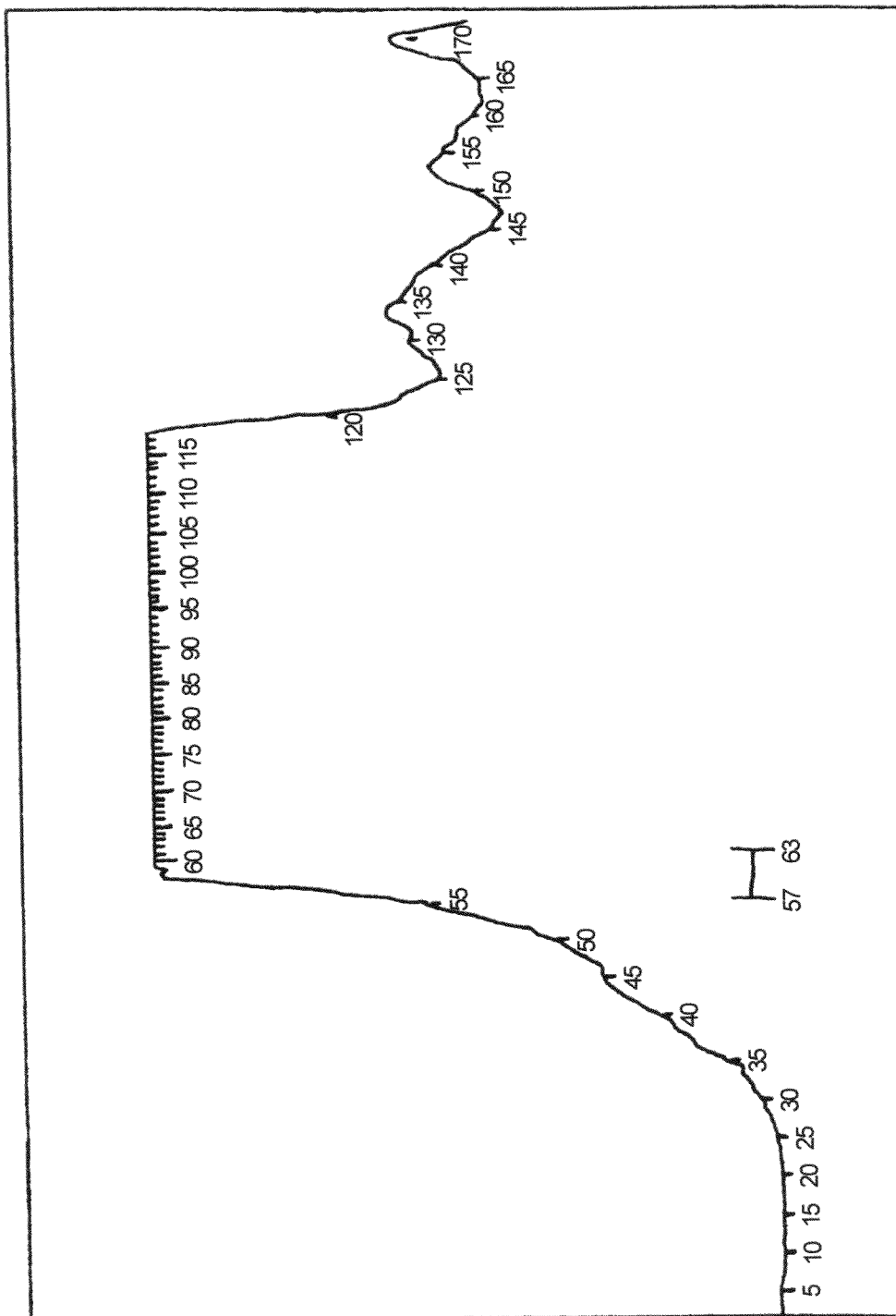
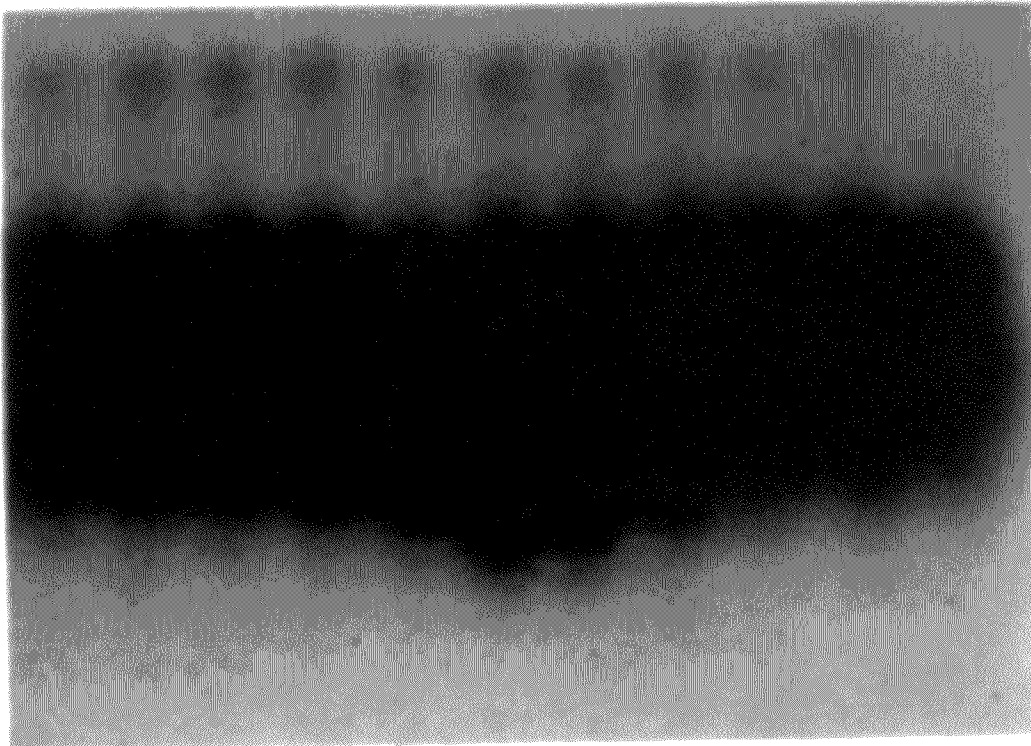


FIG. 6B

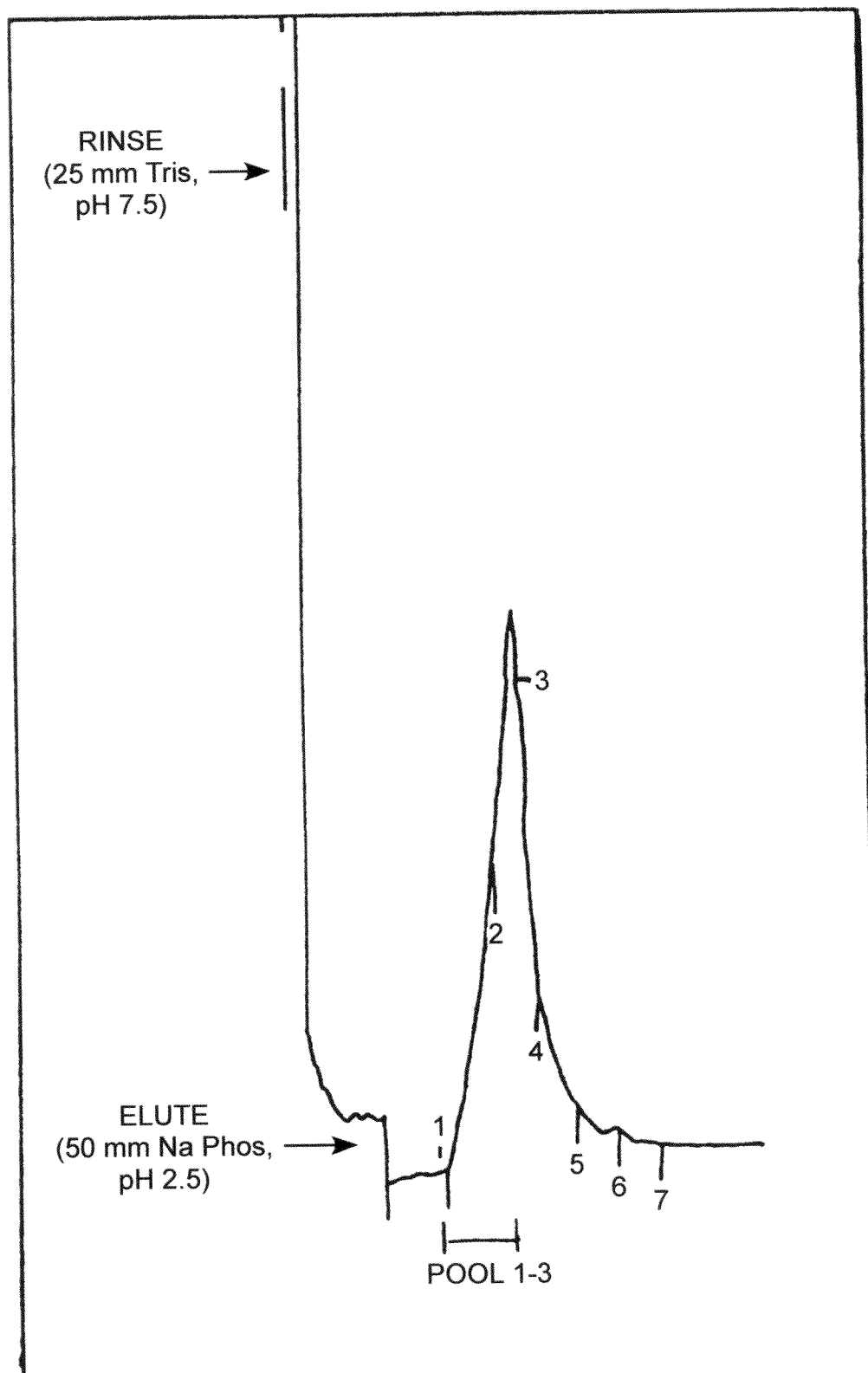
45 47 49 51 53 55 57 59 61 63 65





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FIG. 7





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FIG. 8A

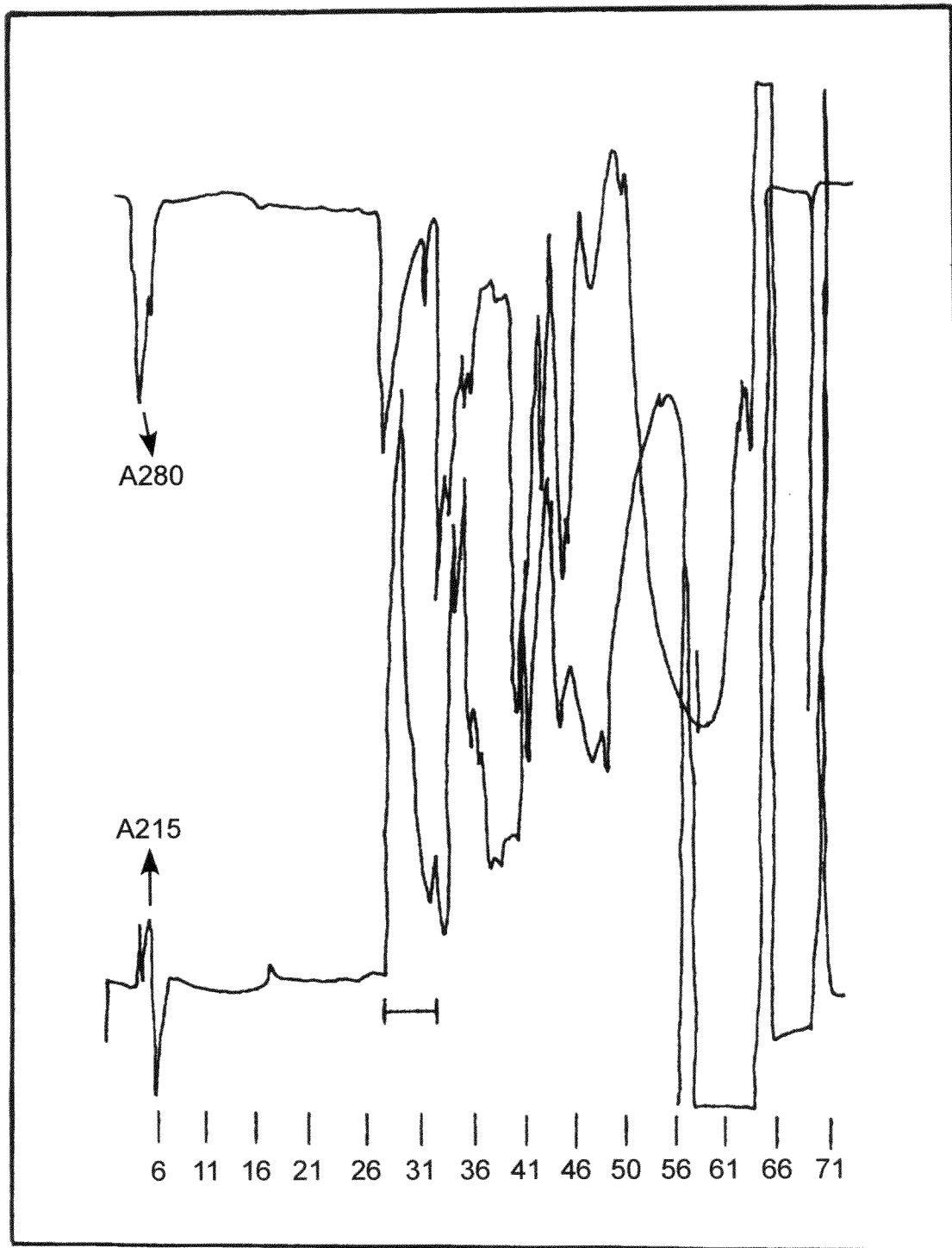
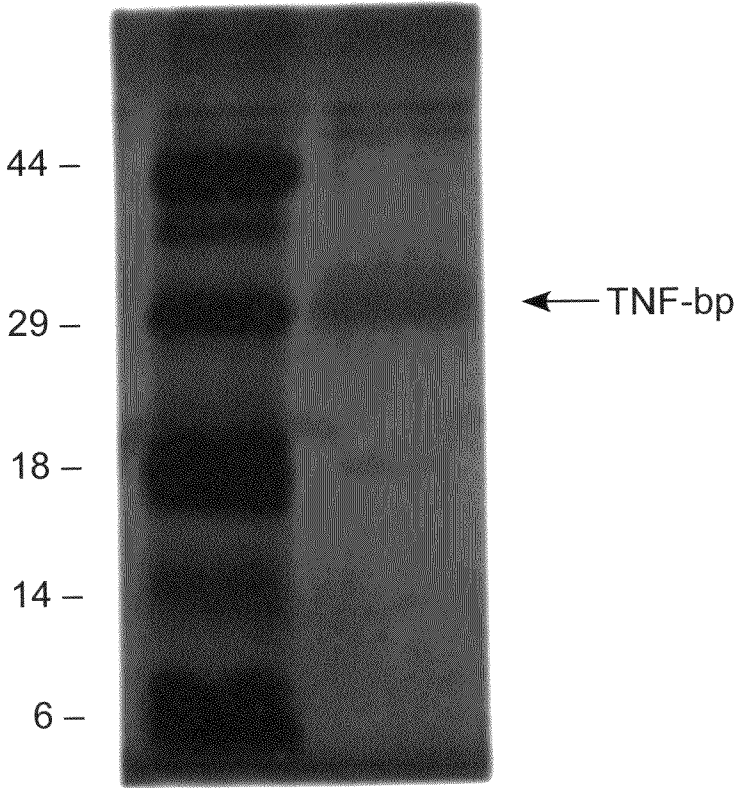


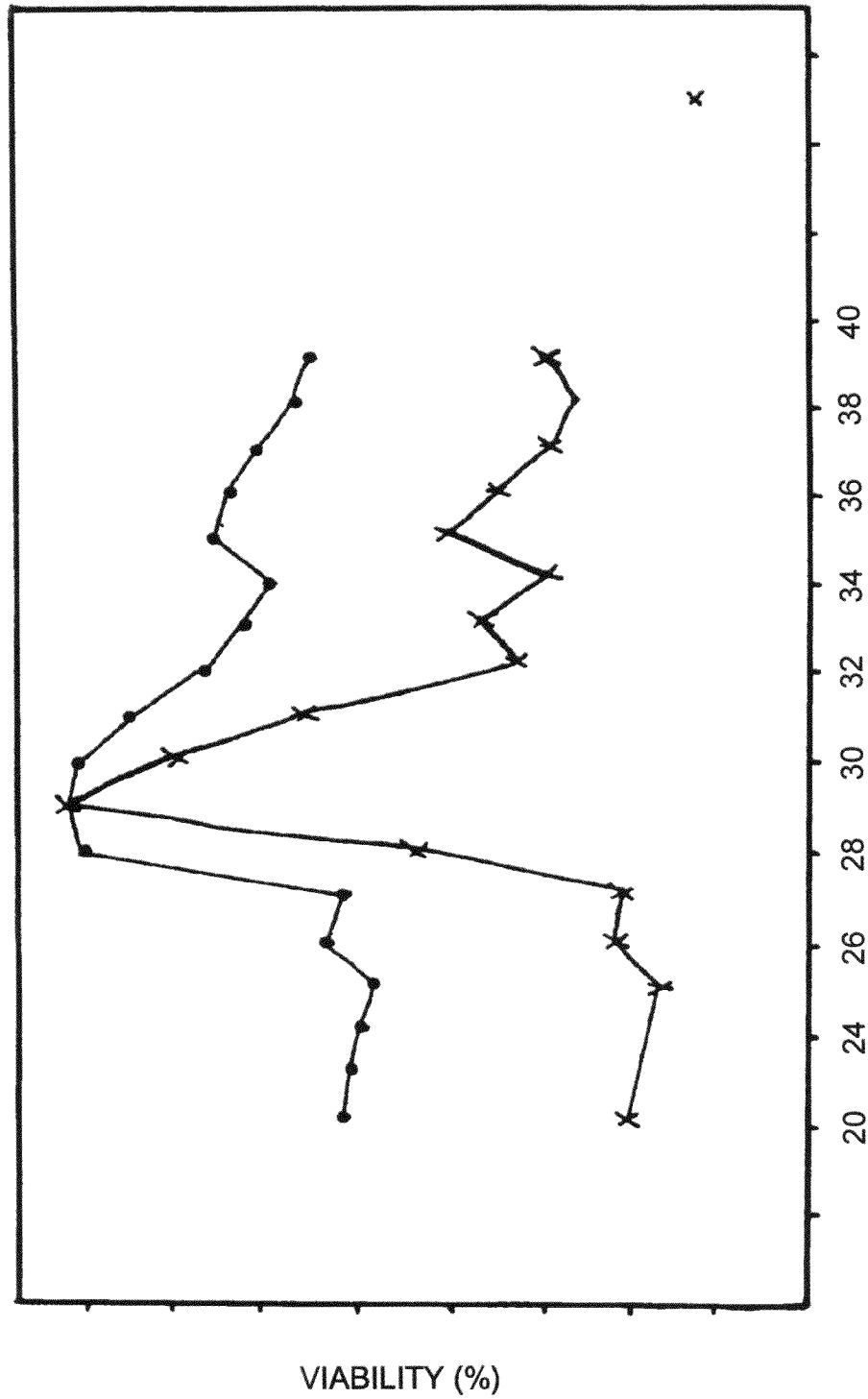
FIG. 8B





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FIG. 8C





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FIG. 9A

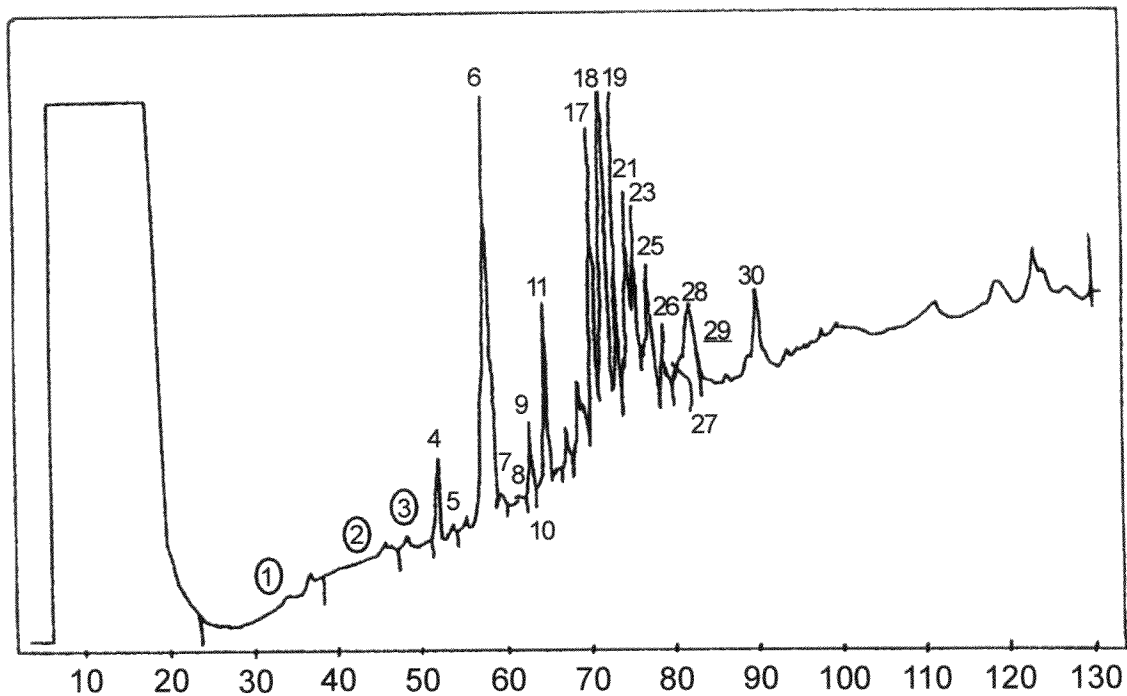
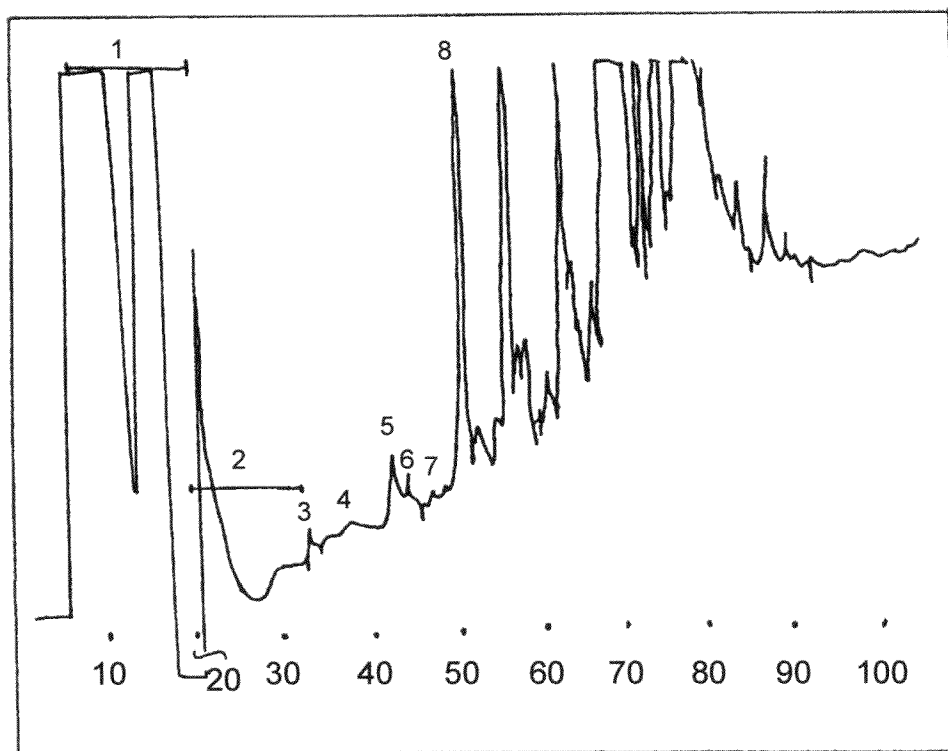


FIG. 9B-1





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FIG. 9B-2

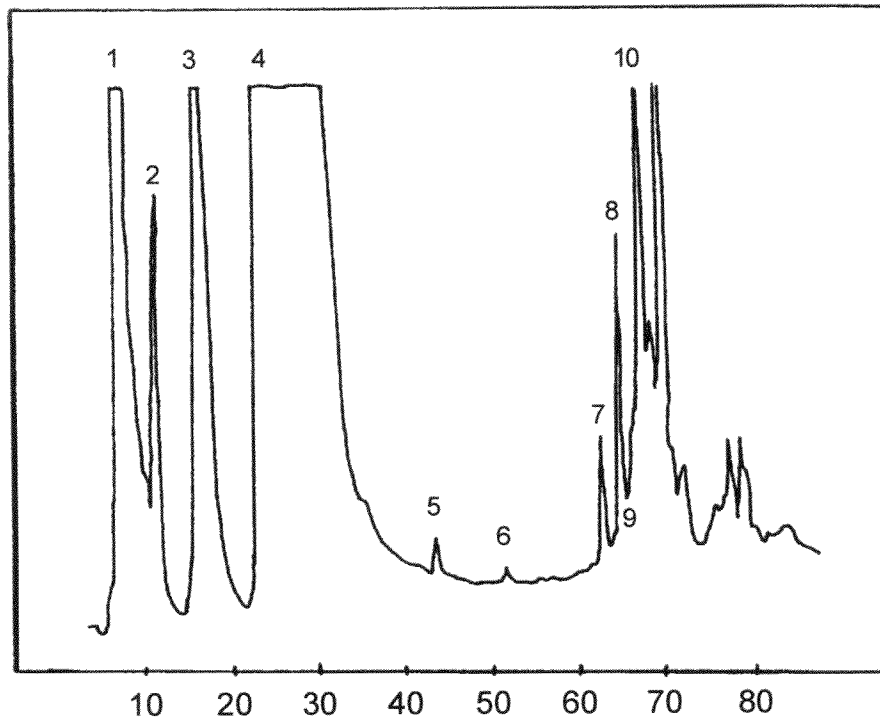
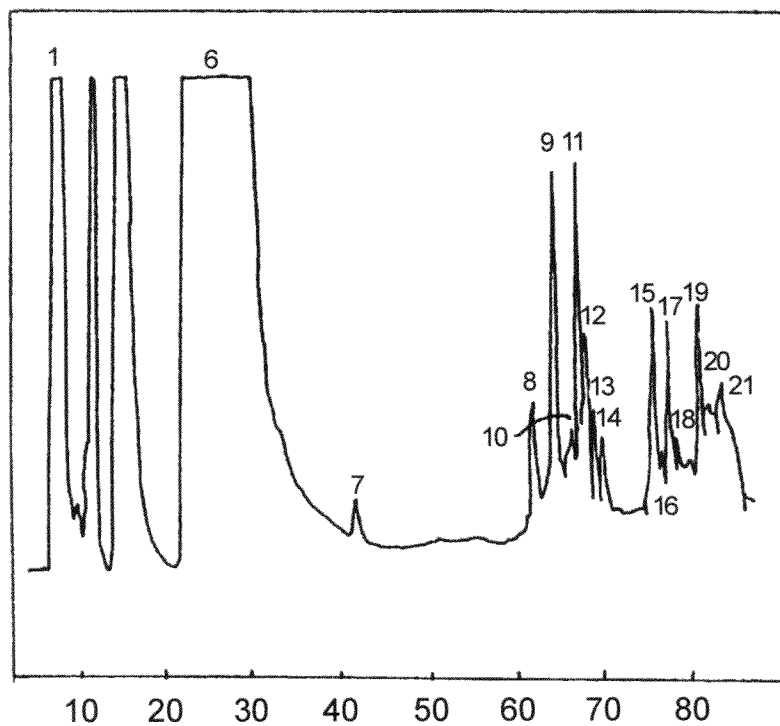


FIG. 9B-3





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FIG. 10A

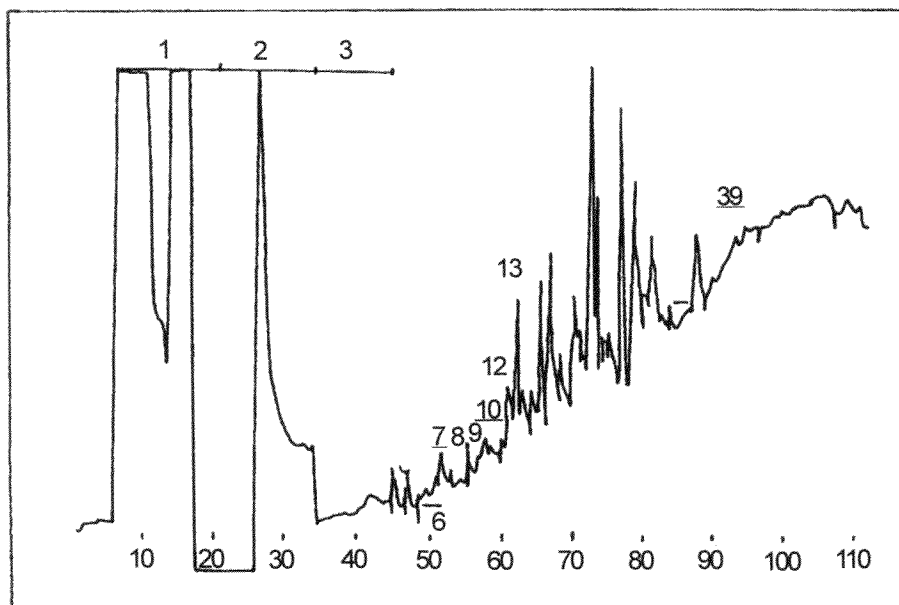
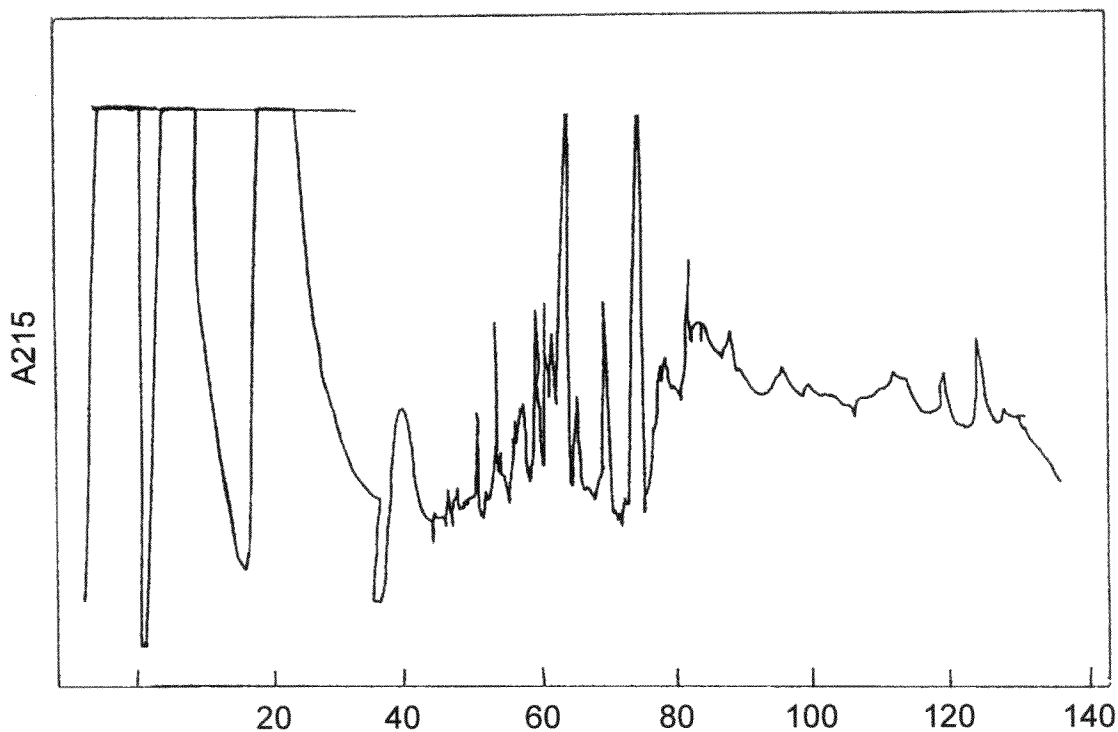


FIG. 10B





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FIG. 11A

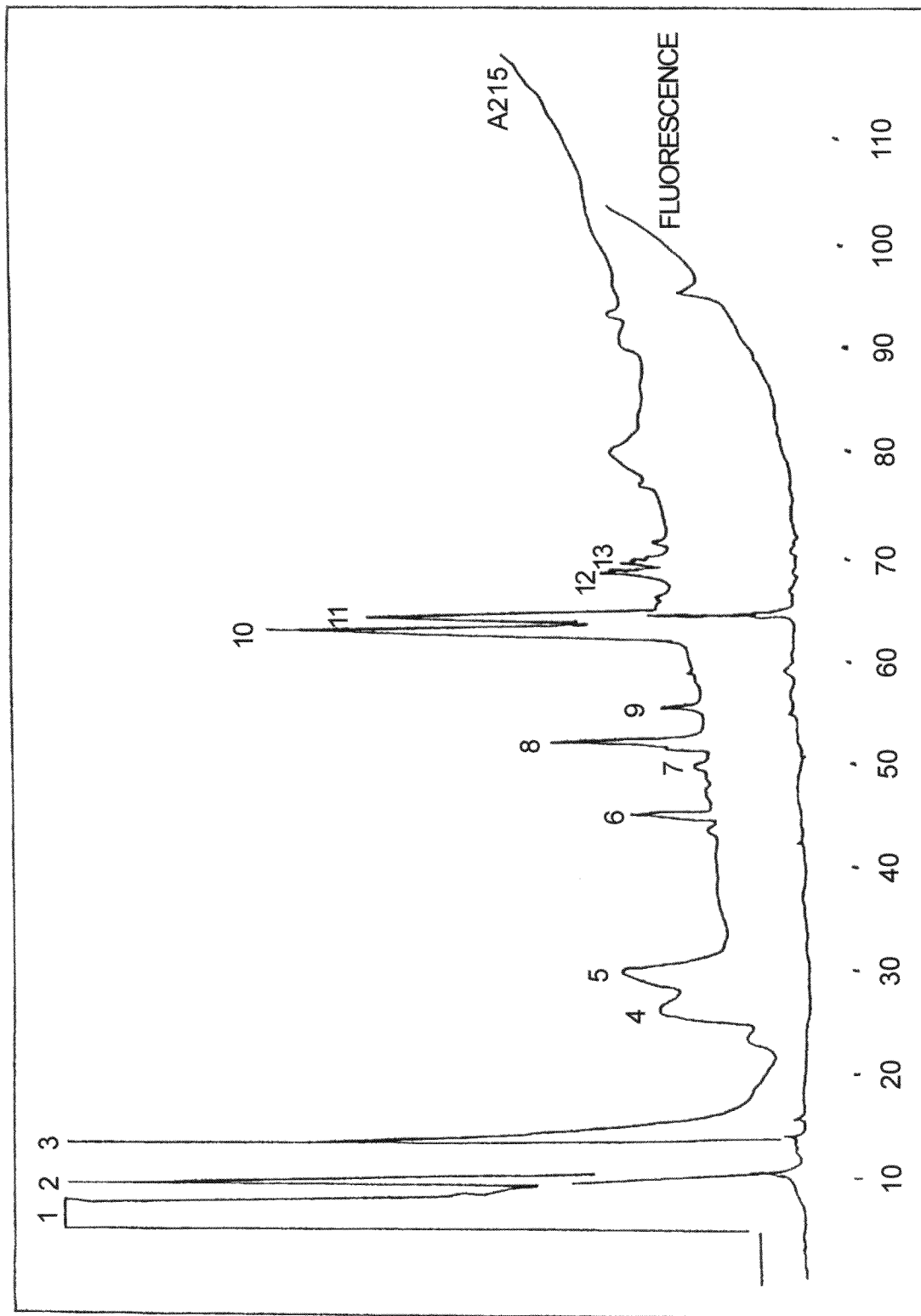
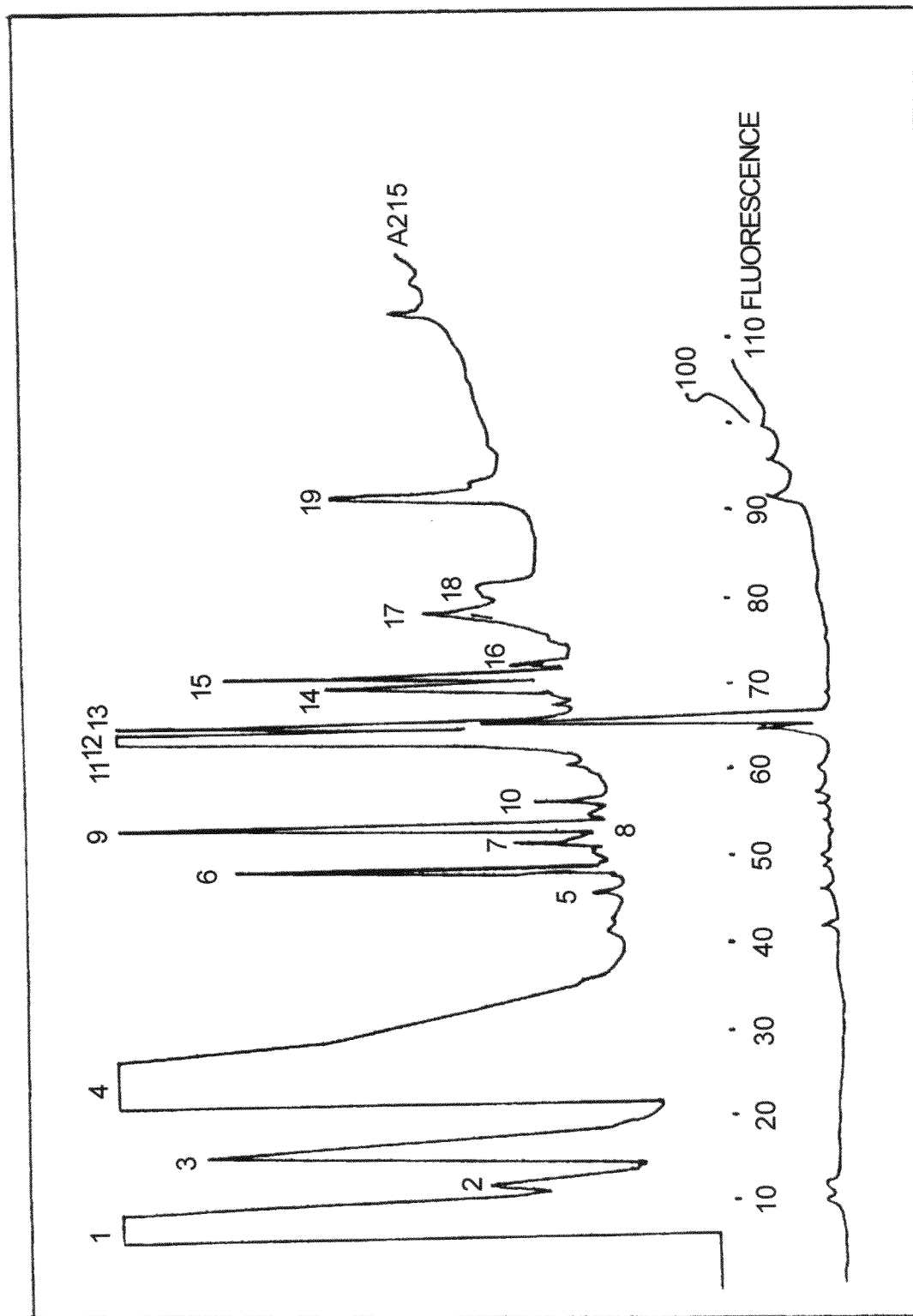




FIG. 11B





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FIG. 12

[illegible]



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FIG. 13B

397	406	415	424	433	444
ATC CAC CCT CAA AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA G GTAGGGCAA					
Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys Ala					
454	464	474	484	494	504
514					
GTGGAAACGG TGAATGCCCT CAGGTCCTGG GTGCTGCTTC TTTCTCTGCT TCTTCCAGTT GTTCTTCCCT					
524	534	544	554	564	574
584					
AACTTTGCTG TCTCTCCTGG GCTGGGATTT TCTCCCTCCC TCCTCTCCTA GAGACTTCAG GGAATCGGCC					
594	604	614	624	634	644
654					
CTGGCTGTTG TCCCTAGCAT GGGCTCCTT CCTTGTGTT TCACCCGCAG CCTAACTCTG CGGCCCCATT					
664	673	682	691	700	
CA CA GGA ACC TAC TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC					
Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp					



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FIG. 13C

709	718	727	736	745	754
TGC AGG GAG TGT GAG AGC AGC TCC TTC ACC GCT TCA GAA AAC CAC CTC AGA CAC					
Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His					
763	772	781	797	807	817
TGC CTC AGC TGC TCC AAA TGC CGA AAG GGTGAGTGTG CACAGGCAGG AGAGTCAGGC					
Cys Leu Ser Cys Ser Lys Cys Arg Lys					
827	837	847	857	867	877
887					887
GGGTCTTGAG TGGTGTGTGG GTGCCCTGTCT ATGTGCAGGC TGGTGGGTGT GGGCAGGAAG GTGTGTGTTT					
897	907	917	927	937	947
957					957
TGGTGGGACA CTGCATGGAT GTGAGTGTGT ATTACAGAGA CACACACTTA GGGGTATGTC AGGAAGGGGA					
967	977	987	997	1007	1016
TGCAGGGACA GGAGGATGCA GGAATCATAC CCCATCTTCT CCCCTCACCA GAA ATG GGT CAG					
					Glu MET Gly Gln
1025					
GTG GAG ATC					
Val Glu Ile					



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FIG. 14

1 20 30 40 50 60 70 80
DSVCPQGKYIHPQNNNSICCTKCHKGTLYNDCPGPGQDTCRECESGSFTASENHLRHCLSCSKCRKEMGQVEISSCTVDRDT
90
VCGCRKN
KQNTVCTCHAGFFLRENECVSC
LECTKLCLPQIEN

FIG. 15

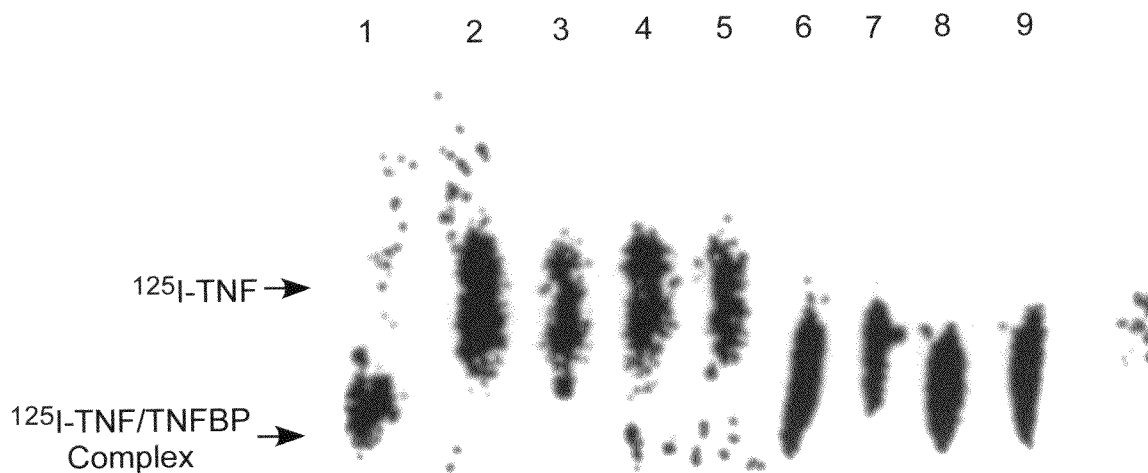


FIG. 16

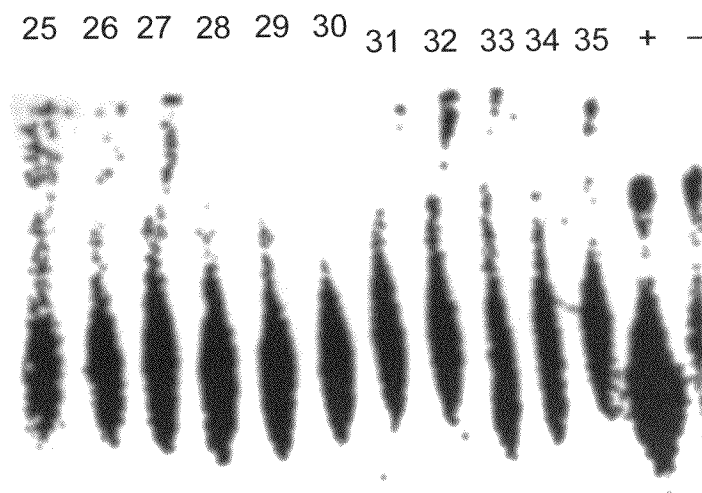


FIG. 17

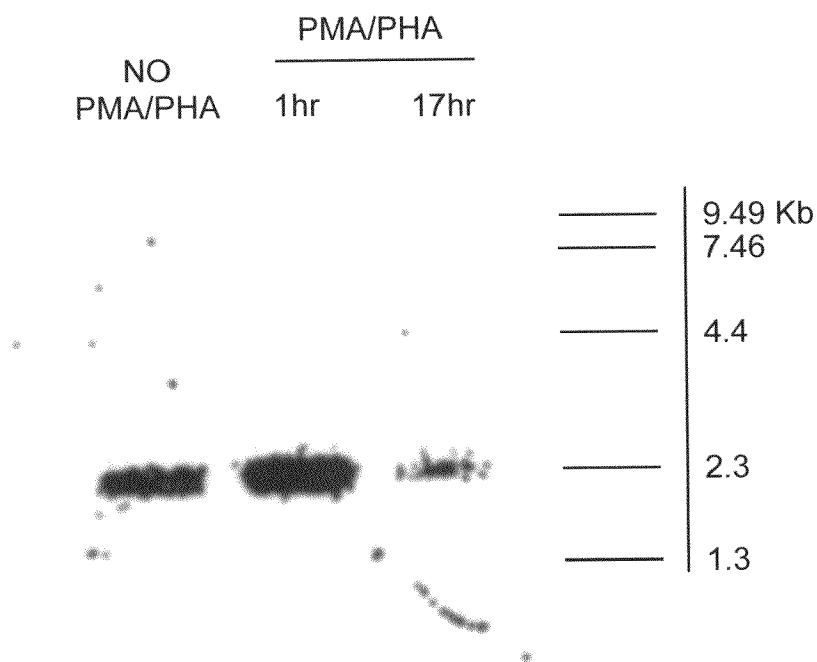
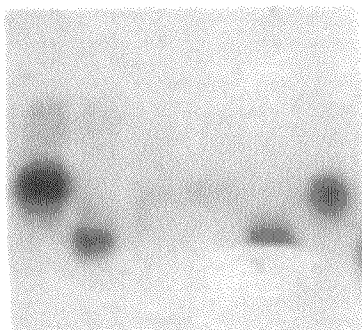


FIG. 18

11 21 51 12 22 52





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FIG. 19

20
Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Ser Ile Cys Cys Thr
40
Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
60
Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu
80
Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp
100
Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu
120
Phe Gln Cys Phe Asn Cys Ser Leu Cys Ser Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
140
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu Asn Glu Cys Val
160
Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile Glu
Asn



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FIG. 20A

[illegible]



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FIG. 20B

531	540	549	558	567	576
GTG GAC CGG GAC ACC GTG TGT GGC TGC AGG AAG AAC CAG TAC CGG CAT TAT TGG	Val Asp Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp				
585	594	603	612	621	630
AGT GAA AAC CTT TTC CAG TGC TGC TGC TGC CTC AAT GGG ACC GTG	Ser Glu Asn Leu Phe Gln Cys Phe Asn Cys Ser Leu Cys Thr Cys His Gly Thr Val				
639	648	657	666	675	684
CAC CTC TCC TGC TGC CAG GAG AAA CAG AAC ACC GTG TGC ACC TGC CAT GCA GGT TTC	His Leu Ser Cys Cys Gln Glu Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe				
693	702	711	720	729	738
TTT CTA AGA GAA AAC GAG TGT GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG	Phe Leu Arg Arg Glu Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu				
747	756	765			
TGC ACG AAG TTG TGC CTA CCC CAG ATT GAG AAT	Cys Thr Lys Lys Leu Cys Leu Pro Gln Ile Glu Asn				



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FIG. 21A

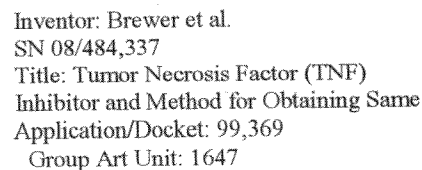
10	20	30	40	50	60	70
GATCACTGGG ACCAGGCCGT GATCTCTATG CCCGAGTCTC AACCCCTCAAC TGTCAACCCCA AGGCACTTGG						
80	90	100	110	120	130	140
GACGTCCTGG ACAGACCGAG TCCCCGGAAG CCCCAGCACT GCCGCTGCCA CACTGCCCTG AGCCCAAATG						
150	160	171	180	189	198	
GGGGAGTGAG AGGCCATAGC TGTCTGGC ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG						
MET Gly Leu Ser Thr Val Pro Asp Leu Leu						
207	216	225	234	243	252	
CTG CCG CTG CTG CTC CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA CGG GTT ATT						
Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile						
261	270	279	288	297	306	
GGA CTG GTC CCT CAC CTA GGG GAC AGG GAG AAG AGA GAT AGT GTG TGT CCC CAA						
Gly Leu Val Pro His Leu Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln						
315	324	333	342	351	360	
GGA AAA TAT ATC CAC CCT CAA AAT AAT TCG ATT TGC ACC AAG TGC CAC AAA						
Gly Lys Tyr Ile His Pro Gln Asn Ser Ile Cys Cys Thr Lys Cys His Lys						



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FIG. 21B

369	GGA ACC	TAC	TTG	TAC	AAT	GAC	TGT	CCA	GGC	CCG	GGG	CAG	GAT	ACG	GAC	TGC	AGG	414
	Gly Thr	Tyr	Leu	Tyr	Asn	Asp	Cys	Pro	Gly	Pro	Gly	Gln	Asp	Thr	Asp	Cys	Arg	
423					432			441			450			459			468	
	GAG	TGT	GAG	AGC	GGC	TCC	TTC	ACC	GCT	TCA	GAA	AAC	CAC	CTC	AGA	CAC	TGC	CTC
	Glu Cys	Glu	Ser	Gly	Ser	Gly	Phe	Thr	Ala	Ser	Glu	Asn	His	Leu	Arg	His	Cys	Leu
477					486			495			504			513			522	
	AGC	TGC	TCC	AAA	TGC	CGA	AAG	GAA	ATG	GGT	CAG	GTG	GAG	ATC	TCT	TCT	TGC	ACA
	Ser Cys	Ser	Ser	Lys	Cys	Arg	Lys	Glu	MET	Gly	Gln	Val	Glu	Ile	Ser	Ser	Cys	Thr
531					540			549			558			567			576	
	GTG	GAC	CGG	GAC	ACC	Thr	Val	Cys	Gly	Arg	Lys	Asn	Gln	Tyr	Arg	His	Tyr	Trp
	Val Asp	Arg	Arg	Asp	Thr	Val	Cys	Gly	Cys	Arg	Lys	Asn	Gln	Tyr	Arg	His	Tyr	Trp
585					594			603			612			621			630	
	AGT	GAA	AAC	CTT	TTC	CAG	TGC	TTC	AAT	TGC	AGC	CTC	TGC	CTC	AAT	GGG	ACC	GTG
	Ser Glu	Asn	Asn	Leu	Phe	Gln	Cys	Phe	Asn	Cys	Ser	Leu	Cys	Leu	Asn	Gly	Thr	Val
639					648			657			666			675			684	
	CAC	CTC	TCC	TGC	CAG	GAG	AAA	CAG	AAC	ACC	GTG	TGC	ACC	TGC	CAT	GCA	GGT	TTC
	His Leu	Ser	Ser	Cys	Gln	Glu	Lys	Gln	Asn	Thr	Val	Cys	Thr	Cys	His	Ala	Gly	Phe



693	702	711	720	729	738
CTA	AGA	GAA	AAC	GAG	GAT
Leu	Arg	Glu	Asn	Glu	Arg
Phe	Arg	Glu	Asn	Glu	Arg
747	750	765	774	783	792
TGC	AAG	TTG	TGC	CTA	CTG
Cys	Thr	Lys	Leu	Cys	Leu
801	810	819	828	837	846
GGC	ACC	ACA	GTG	CTG	CTG
Gly	Thr	Thr	Val	Val	Val
855	864	873	882	891	900
CTC	TTC	ATT	GGT	TTA	ATG
Leu	Leu	Phe	Ile	Gly	Leu
909	918	927	936	945	954
TCC	ATT	GTT	TGT	GGG	AAA
Ser	Ile	Val	Cys	Gly	Lys
963	972	981	990	999	1008
ACT	ACT	AAG	CCC	CTG	CTG
Thr	Thr	Lys	Pro	Leu	Ala



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FIG. 21D

1017	1026	1035	1044	1053	1062
CCC ACC CTG GGC TTC AGT CCC GTG CCC AGT TTC ACC TCC ACC TCC ACC	Pro Thr Leu Gly Phe Ser Pro Val Pro Ser Thr Phe Thr Ser Ser Ser Thr				
1071	1080	1089	1098	1107	
1116					
TAT ACC CCC GGT GAC TGT CCC AAC TTT GCG GCT CCC CGC AGA GAG GTG GCA CCA	Tyr Thr Pro Gly Asp Cys Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro				
1125	1134	1143	1152	1161	1170
CCC TAT CAG GGG GCT GAC CCC ATC CTT GCG ACA GCC CTC GCC TCC GAC CCC ATC	Pro Tyr Gln Gly Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile				
1179	1188	1197	1206	1215	1224
CCC AAC CCC CTT CAG AAG TGG GAG GAC AGC GCC CAC AAG CCA CAG AGC CTA GAC	Pro Asn Pro Leu Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp				
1233	1242	1251	1260	1269	1278
ACT GAT GAC CCC GCG ACG CTG TAC GCC GTG GTG GAG AAC AAC GTG CCC CCG TTG CGC	Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro Leu Arg				
1287	1296	1305	1314	1323	1332
TGG AAG GAA TTC GTG CGG CGC CTA GGG CTG AGC GAC CAC GAG ATC GAT CGG CTG	Trp Lys Glu Phe Val Arg Arg Arg Leu Gly Leu Ser Asp His Glu Ile Asp Arg Leu				



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FIG. 21E

1341	1350	1359	1368	1377	1386
CTG CAG AAC GGG CGC TGC CTG CGC GAG GCG CAA TAC AGC ATG CTG GCG ACC					
Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln Tyr Ser MET Leu Ala Thr					
1395	1404	1413	1422	1431	1440
TGG AGG CGG CGC ACG CCG CGG CGC GAG GCG GCC ACG CTG GAG CTG GGA CGC GTG					
Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala Thr Leu Glu Leu Arg Val					
1449	1458	1467	1476	1485	1494
CTC CGC GAC ATG GAC CTG CTG GGC TGC CTG GAG GAC ATC GAG GAG GCG CTT TGC					
Leu Arg Asp MET Asp Leu Leu Gly Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys					
1503	1512	1521	1530	1546	1556
GGC CCC GCC CTC CCG CCC CCG CCC AGT CTT CTC AGA TGA GGCTGCGCCC CTGCGGGCAG					
Gly Pro Ala Ala Leu Pro Pro Ala Pro Ser Leu Leu Arg					
1566	1576	1586	1596	1606	1616
CTCTAAGGAC CGTCCTGCCG GATCGCCTTC CAACCCCACT TTTTCTTCTGA AAGGAGGGGT CCTGCAGGGG					
1636	1646	1656	1666	1676	1686
CAAGCAGGAG CTAGCAGCCG CCTACTTGGT GCTAACCCCT CGATGTACAT AGCTTTTCTC AGCTGCCTGC					



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FIG. 21F

1706	1716	1726	1736	1746	1756	1766
GCGCCGCCGA	CAGTCAGCGC	TGTGCGCGCG	GAGAGAGGTG	CGCCGTGGGC	TCAAGAGCCT	GAGTGGGTGG
1776	1786	1796	1806	1816	1826	1836
TTTGCGAGGA	TGAGGGACGC	TATGCCCTCAT	GCCCGTTTGT	GGTGTCCTCA	CCAGCAAGGC	TGCTCGGGGG
1846	1856	1866	1876	1886	1896	1906
CCCCTGGTTC	GTCCCTGAGC	CTTTTTCACA	GTGCATAAGC	AGTTTTTTTT	GTTTTTGT	TGTTTTGTTT
1916	1926	1936	1946	1956	1966	1976
TGTTTTTAAA	TCAATCATGT	TACACTAATA	GAAACTTGGC	ACTCCTGTGC	CCTCTGCCCTG	GACAAGCACA
1986	1996	2006	2016	2026	2036	2046
TAGCAAGCTG	AACGTGTCCTA	AGGCAGGGGC	GAGCACGGAA	CAATGGGGCC	TTCAGCTGGA	GCTGTGGACT
2056	2066	2076	2086			
TTTGACATA	CACTAAAAAT	CTGAAGTTAA	AGCTCAAAAA	AA		



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FIG. 22

GA ATT CCA CAA CGG TTT CCC TCT AGA AAT AAT TTT GTT TAA CTT TAA GAA GGA GAT ATA CAT

Start gene 10 protein

sequence

ATG GCT AGC ATG ACT GGT GGA CAG CAA ATG GGT ACG GAT CCG ATC TTG GAG GAT GAT TAA

Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Thr Asp Pro Ile Leu Glu Asp Asp stop

Translational coupler

ATG GAC AGC GTT TGC CCC

Met Asp Ser Val Cys Pro

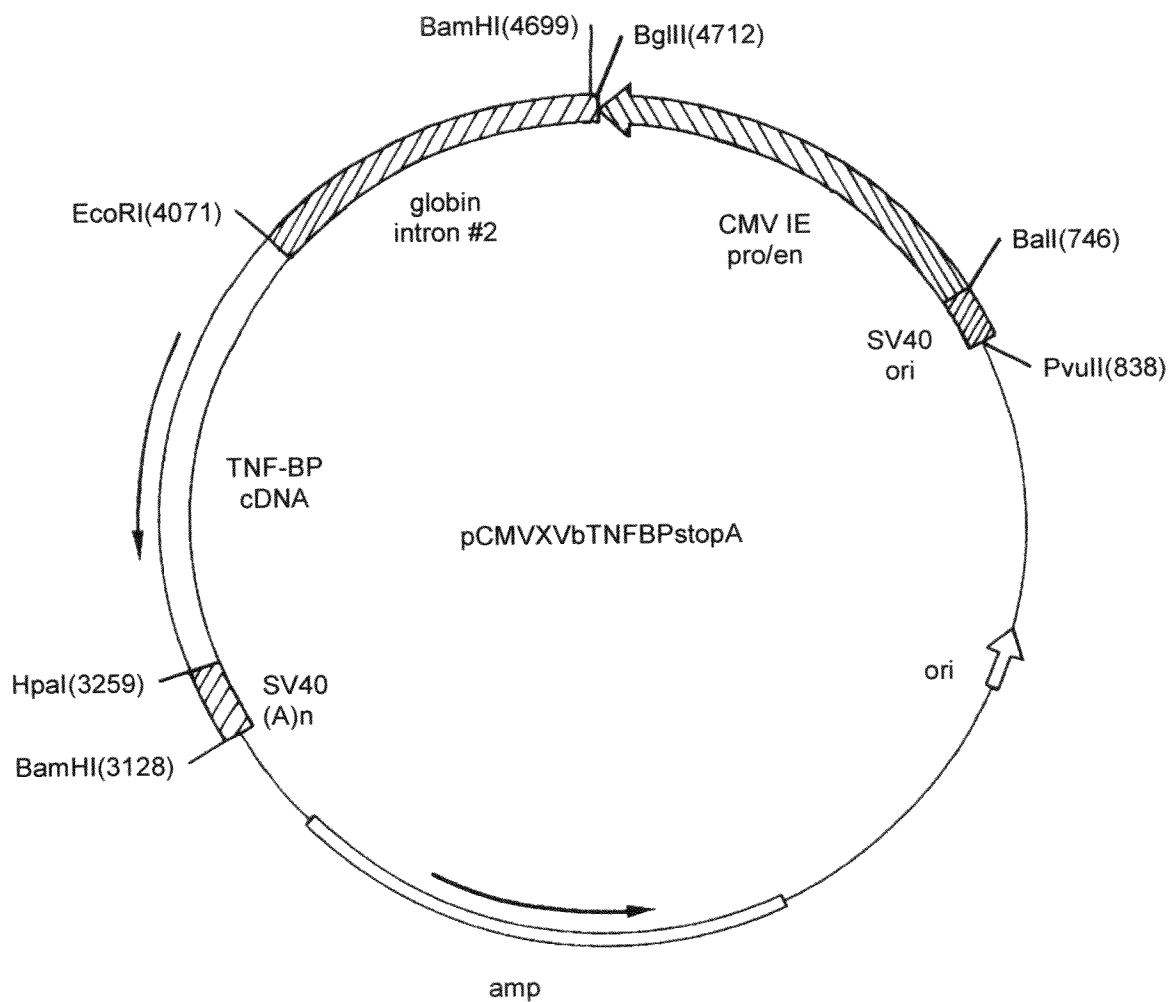
Start TNF inhibitor

sequence



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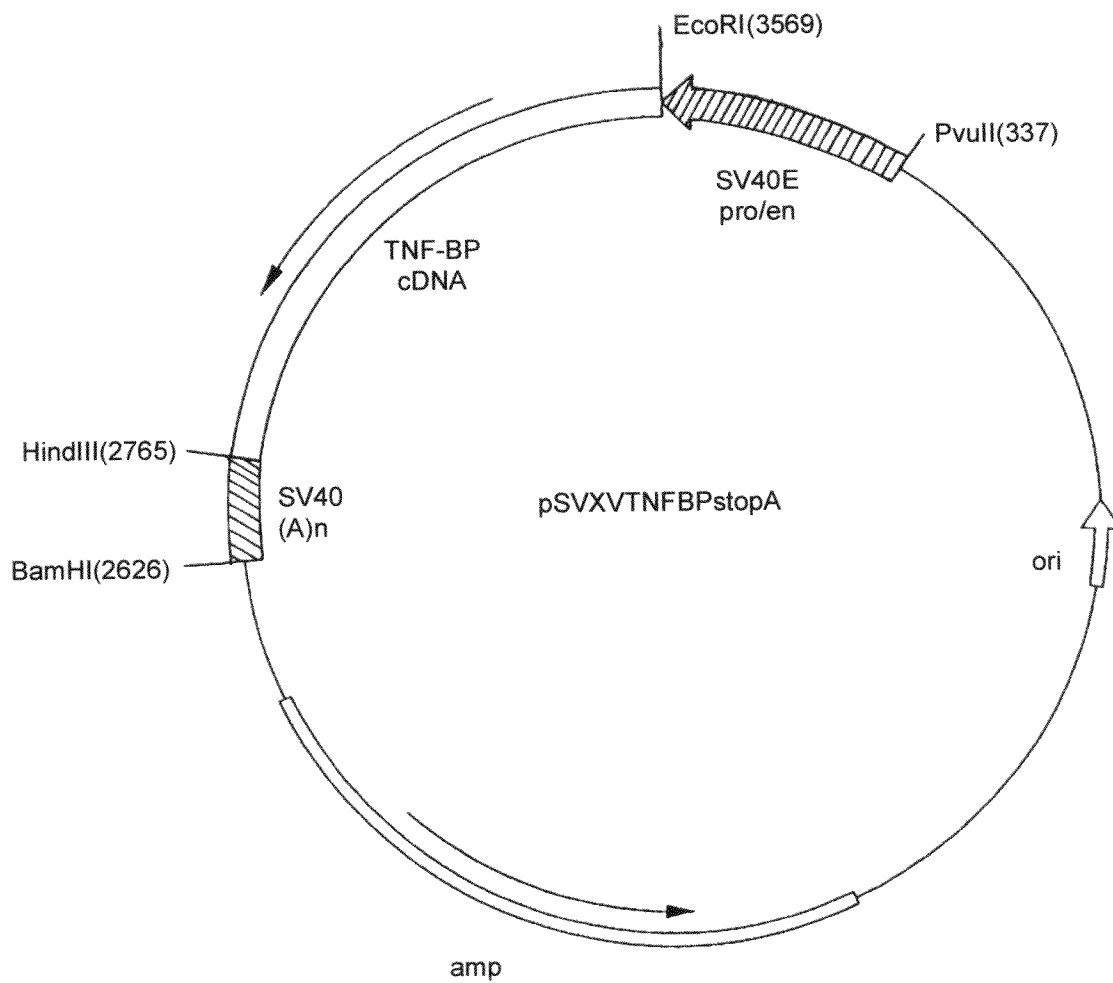
FIG. 23





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FIG. 24





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FIG. 25

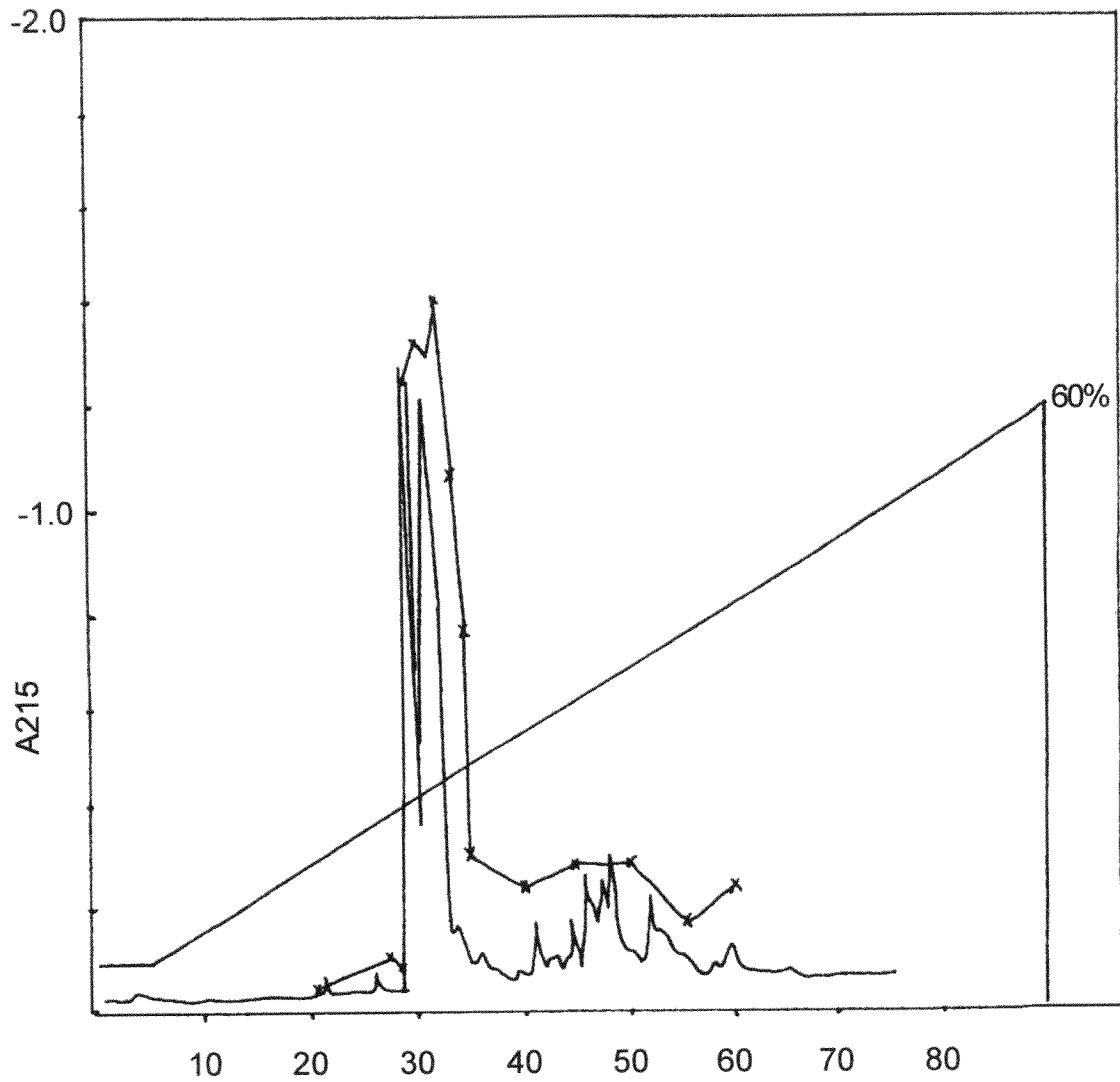
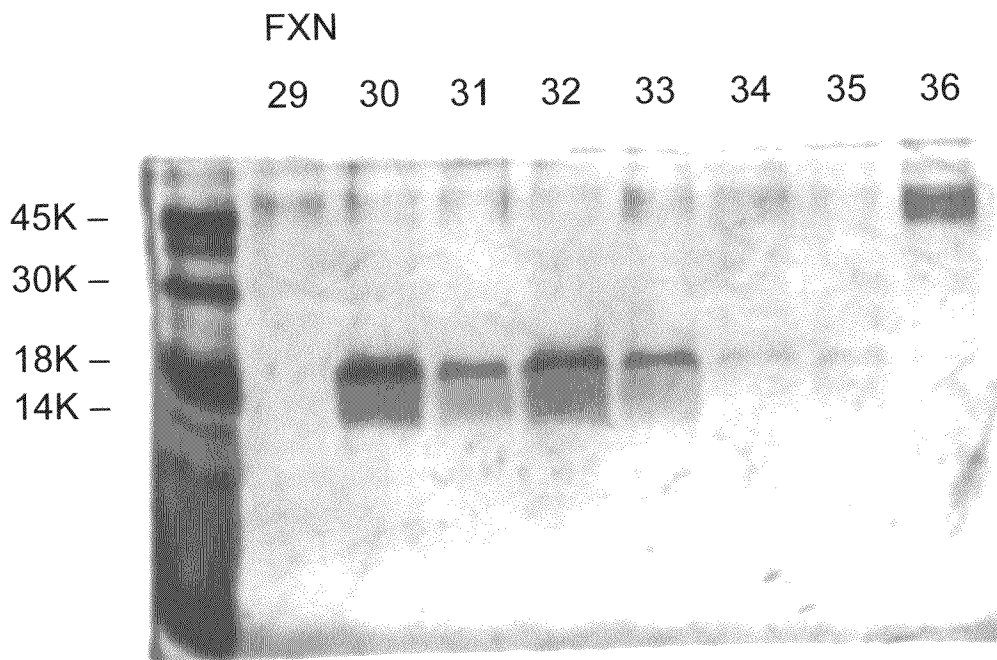


FIG. 26





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FIG. 27

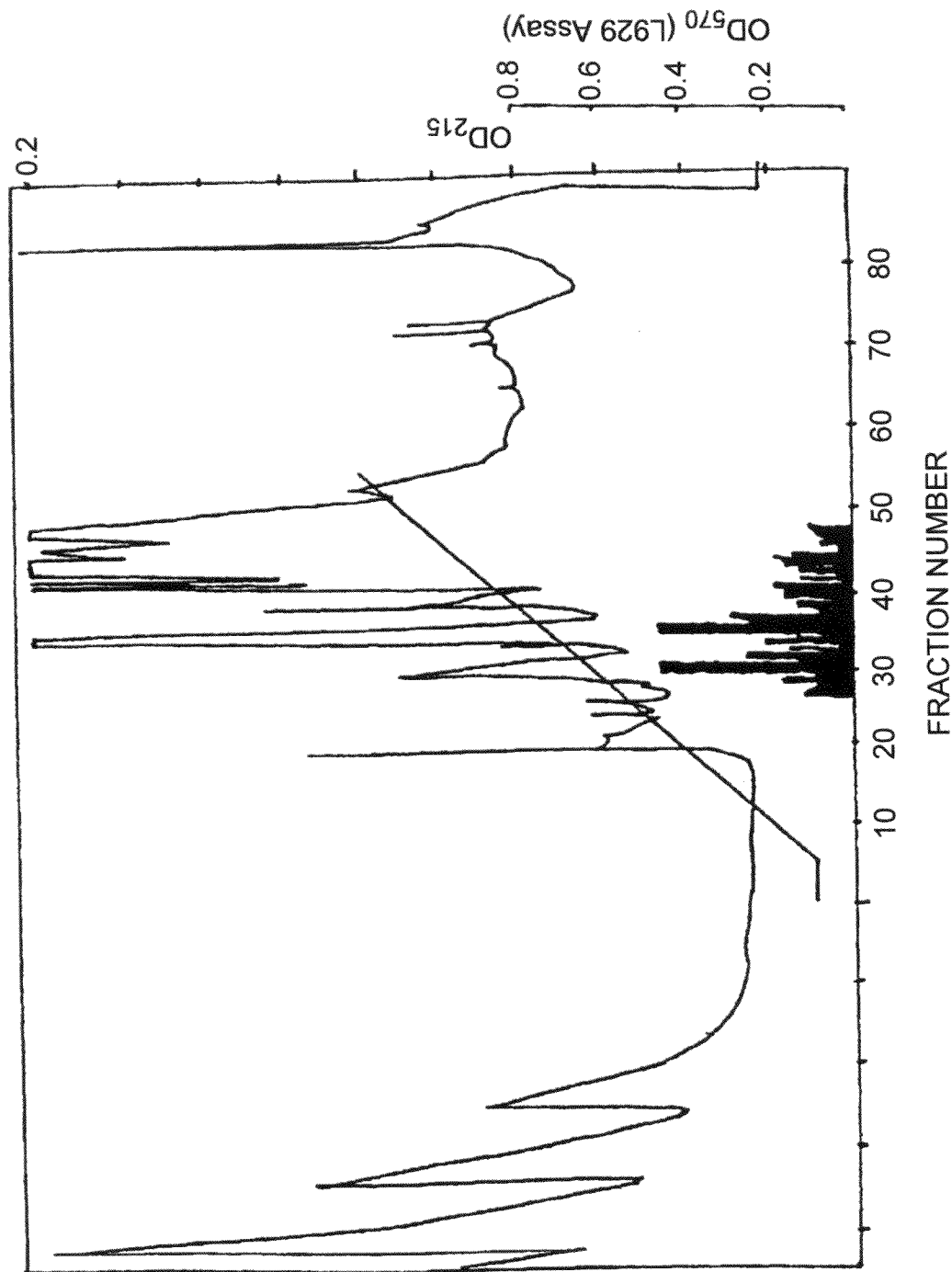
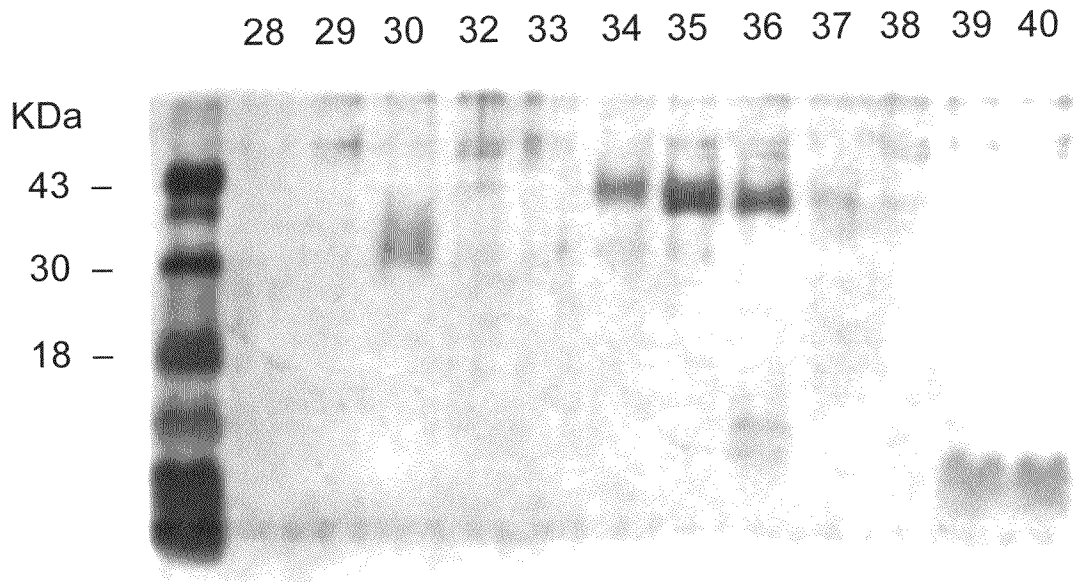


FIG. 28





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FIG. 29

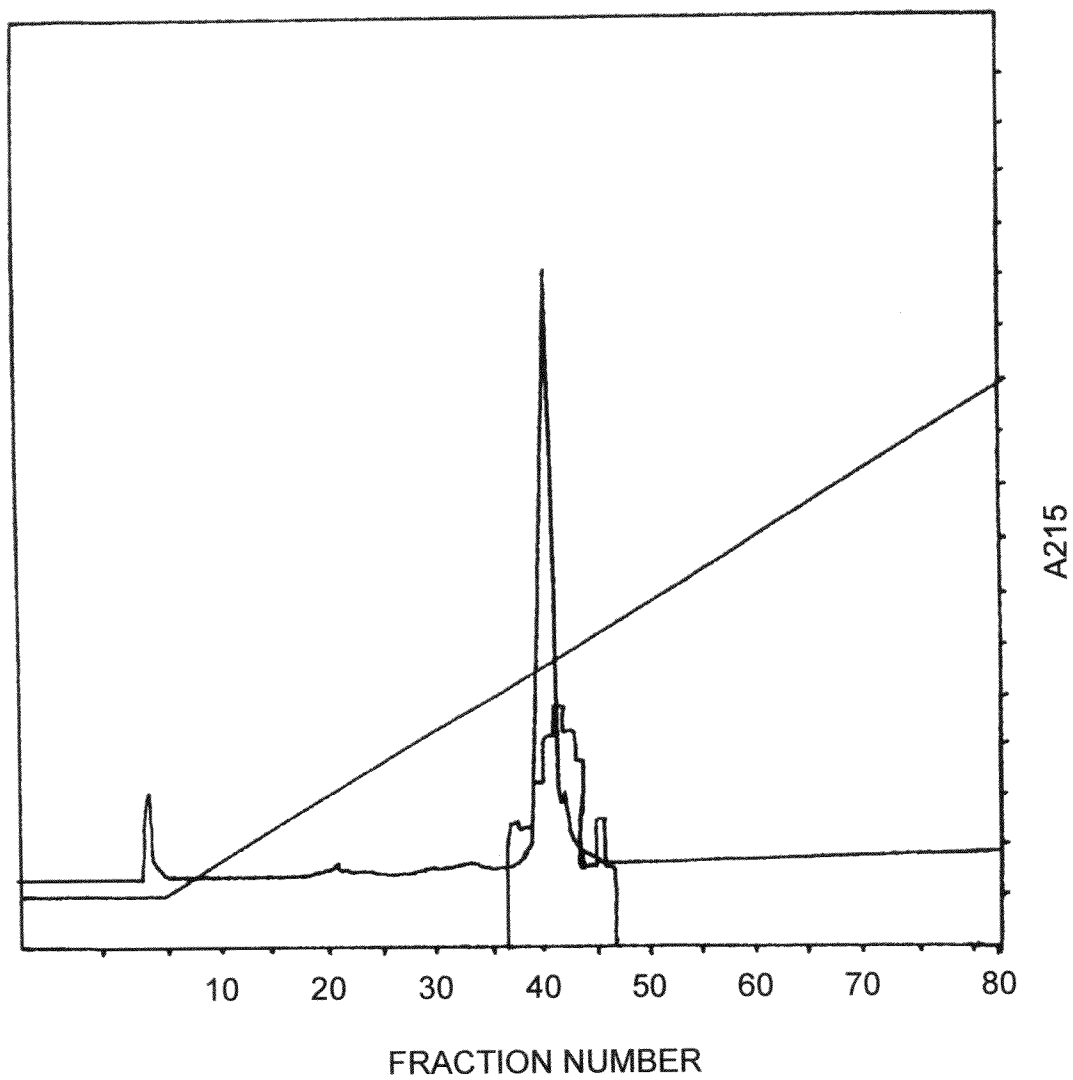
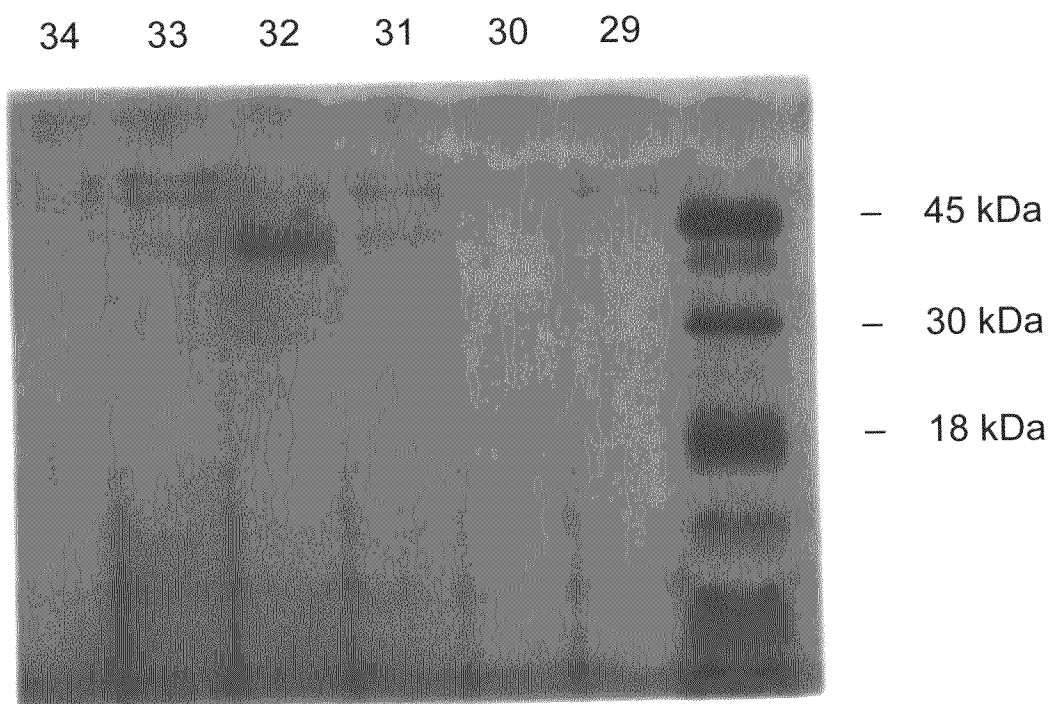


FIG. 30





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FIG. 31

U937-derived TNF inhibitor1 (30 kDa)

()-()-Val-()-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-()-Asn-()-Ile-

U937-derived TNF inhibitor2 (40 kDa)

Leu-Pro-Ala-Gln-Val-Ala-Phe-Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys-Arg-
Leu-Arg-Glu-Tyr-Tyr-Asp-Gln-Thr-Ala-Gln-Met-Cys-Cys-Ser-Lys-Cys-

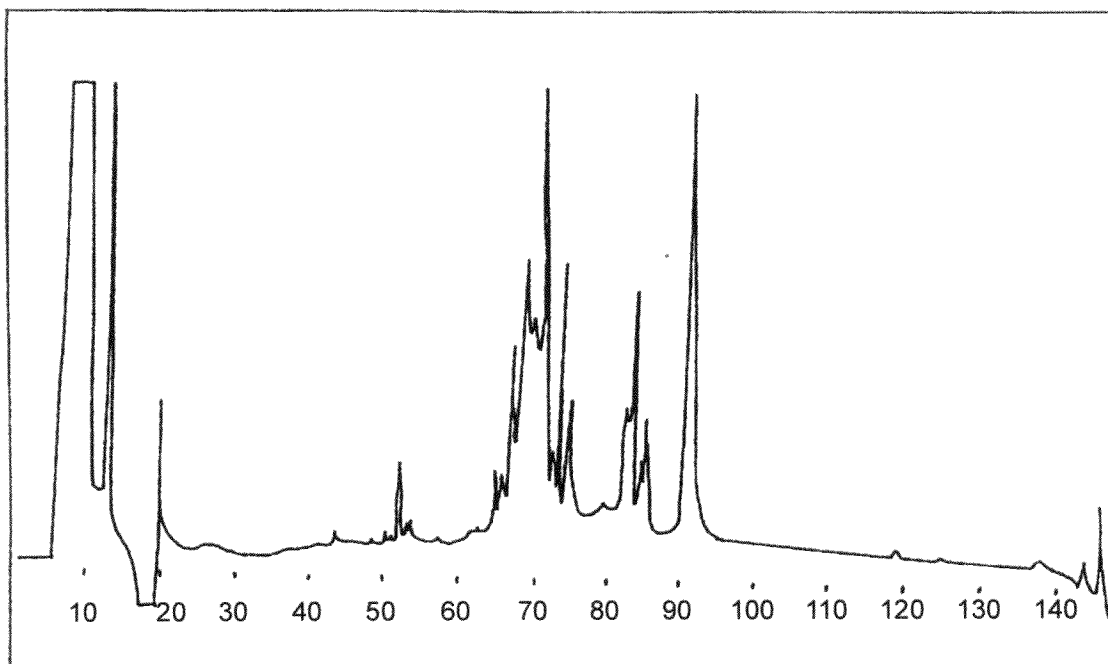
Urine-derived TNF inhibitor2 (40 kDa)

Ala-Gln-Val-Ala-Phe-Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys-()-Leu-()-
Glu-



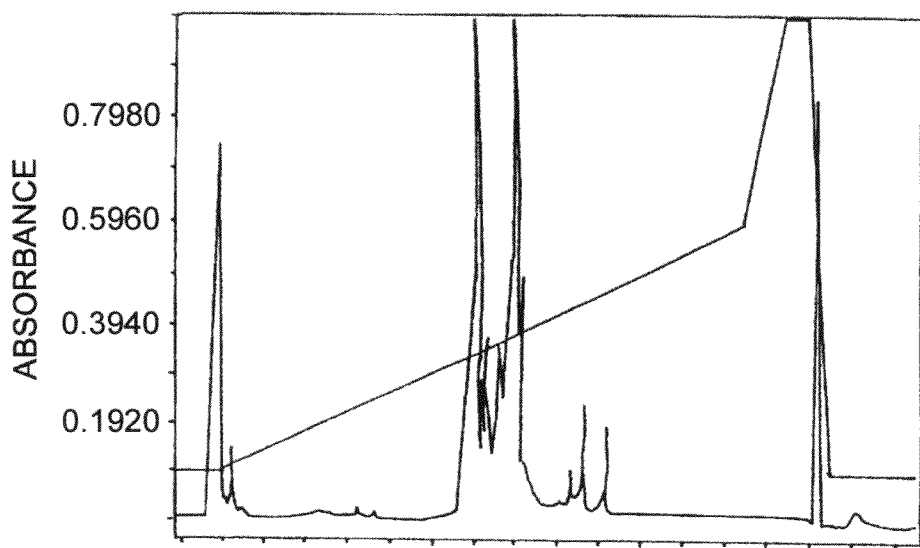
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FIG. 32



V8 DIGEST

FIG. 33



Arg.C A215



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FIG. 34

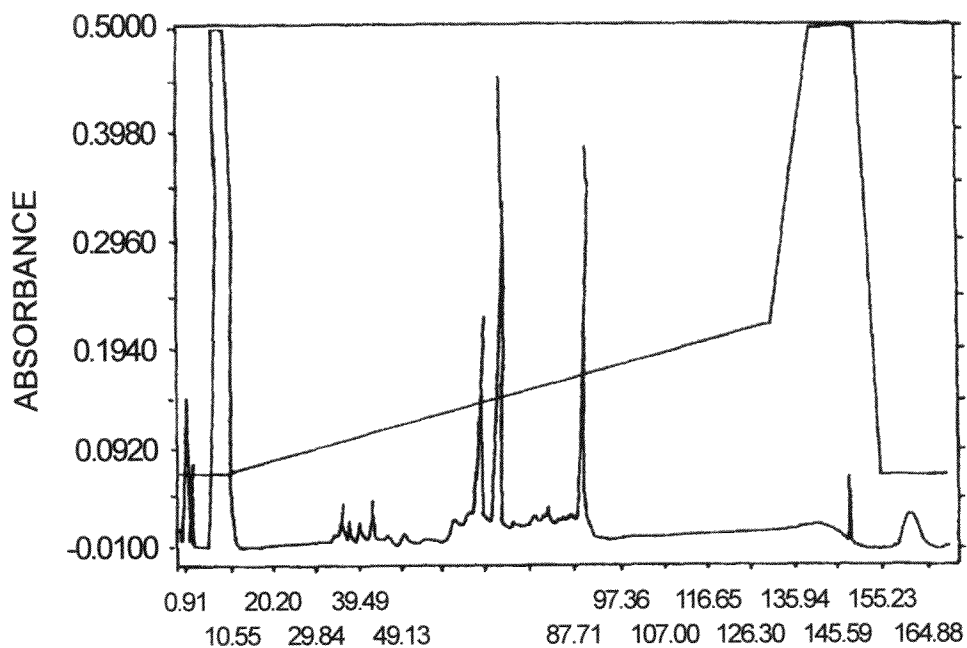
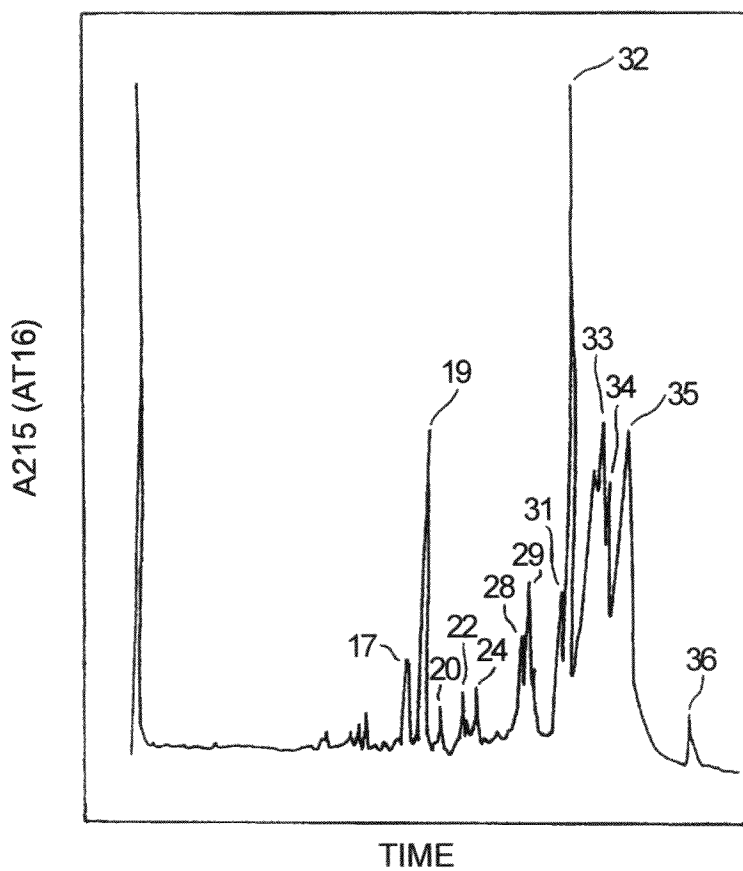


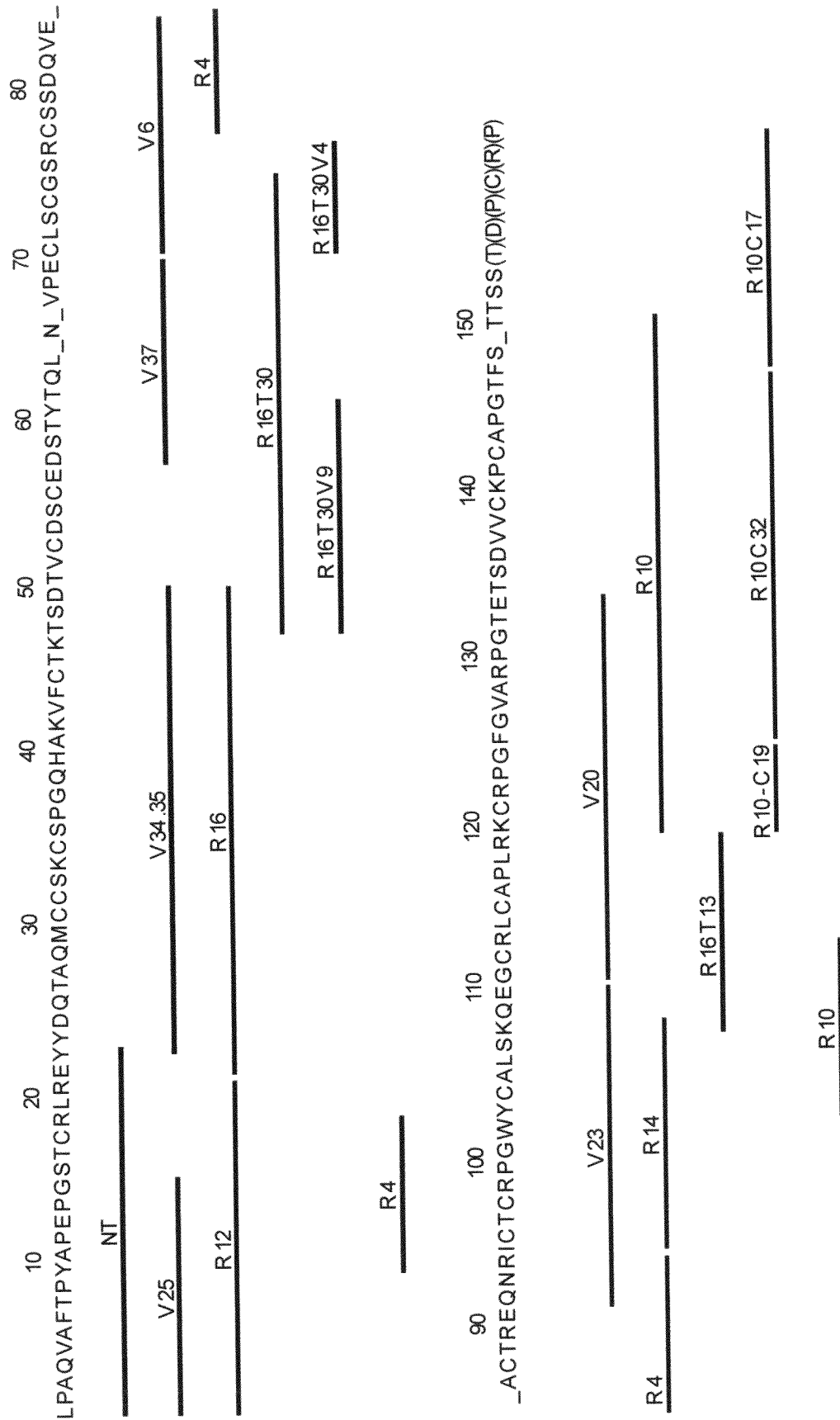
FIG. 35





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FIG. 36





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FIG. 37

	200	209	218	227	
	CCG GAG CCC GGG AGC ACA TGC CGG CTC AGA GAA TAC TAT GAC				
	Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp				
236	245	263	272	281	
	CAG ACA GCT CAG ATG TGC TGC AGC AAG TGC TCG CCG GGC CAA CAT GCA AAA GTC				
	Gln Thr Ala Gln MET Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val				
290	299	317	326	335	
	TTC TGT ACC AAG ACC TCG GAC ACC GTG TGT TGT TGT GAG GAC AGC ACA TAC				
	Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr				
344	353	371	380	389	
	ACC CAG CTC TGG AAC TGG GTT CCC GAG TGC TGC TTG AGC TCC TCC CGC TGT AGC				
	Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser				
398	407	425	434	443	
	TCT GAC CAG GTG GAA ACT CAA GCC TGC TGC ACT CGG GAA CAG AAC CGC ATC TGC ACC				
	Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys Thr				
452	461	470			
	TGC AGG CCC GGC TGG TAC TGC				
	Cys Arg Pro Gly Trp Tyr Cys				



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FIG. 38

Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser
Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys
Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro
Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Arg Asp Ala
Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp



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FIG. 39A

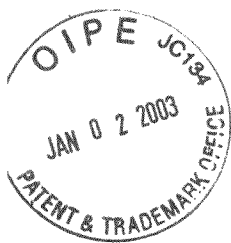
	10	20	30	40	50	60	70
	GAATTCTGGCG CAGCGGAGCC TGGAGAGAAG GCGCTGGGCT GCGAGGGCGC GAGGGCGCGA GGCAGGGGG						
	80	90	101	110	119		
	CAACCGGACC CCGCCCGCAC CC ATG GCG CCC GTC GCC GTC TGG GCC GCG CTG GCC MET Ala Pro Val Ala Val Trp Ala Ala Leu Ala						
128	137	146	155	164	173		
GTC GGA CTG GAG CTC TGG GCT GCG GCG CAC GCC TTG CCC GCC CAG GTG GCA TTT							
Val Gly Leu Glu Leu Trp Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe							
182	191	200	209	218	227		
ACA CCC TAC CCC CCS GAG CCC GCG CCC AGC ACA ICC CGG CTC ABA BAA TAC TAT SAC							
Thr Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp							
236	245	254	263	272	281		
CAG ACA GCT CAG ATG TGC TGC AGC AAG TGC TCG CCG GGC CAA CAT GCA AAA GTC							
Gln Thr Ala Gln MET Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val							
290	299	308	317	326	335		
TTC TGT ACC AAG ACC ACC GTG TGT TGT TGT TGT TGT TGT TGT TGT TGT TGT TGT							
Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr							



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FIG. 39B

[illegible]



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FIG. 39C

614	623	632	641	650	659												
TCA	TCC	ACG	GAT	ATT	TGC	AGG	CCC	CAC	CAG	ATC	TGT	AAC	GTG	GTG	GCC	ATC	CCT
Ser	Ser	Thr	Asp	Ile	Cys	Arg	Pro	His	Gln	Ile	Cys	Asn	Val	Val	Ala	Ile	Pro
668	677	686	695	704	713												
GGG	AAT	GCA	AGC	AGG	GAT	GCA	GTC	TGC	ACG	TCC	ACG	TCC	CCC	ACC	CGG	AGT	ATG
Gly	Asn	Ala	Ser	Arg	Asp	Ala	Val	Cys	Thr	Ser	Thr	Ser	Pro	Thr	Arg	Ser	MET
722	731	740	749	758	767												
GCC	CCA	GGG	GCA	GTA	CAC	TTA	CCC	CAG	CCA	GTG	TCC	ACA	CGA	TCC	CAA	CAC	ACG
Ala	Pro	Gly	Ala	Val	His	Leu	Pro	Gln	Pro	Val	Ser	Thr	Arg	Ser	Gln	His	Thr
776	785	794	803	812	821												
CAG	CCA	ACT	CCA	GAA	CCC	AGC	ACT	GCT	CCA	AGC	ACC	TCC	TTC	CTG	CTC	CCA	ATG
Gln	Pro	Thr	Pro	Glu	Pro	Ser	Thr	Ala	Pro	Ser	Thr	Ser	Phe	Leu	Leu	Pro	MET
830	839	848	857	866	875												
GGC	CCC	AGC	CCC	CCA	GCT	GAA	GGG	AGC	ACT	GGC	GAC	TTC	GCT	CTT	CCA	GTT	GGA
Gly	Pro	Ser	Pro	Pro	Ala	Glu	Gly	Ser	Thr	Gly	Asp	Phe	Ala	Leu	Pro	Val	Gly



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FIG. 39D

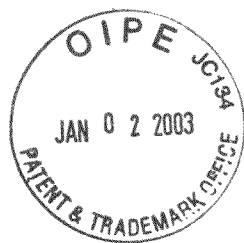
884	893	902	911	920	929
CTG ATT GTG GGT GTG ACA GCC TTG GGT CTA ATA ATA GGA GTG GTG AAC TGT	Leu Ile Val Gly Thr Ala Leu Gly Leu Ile Ile Gly Val Val Asn Cys				
938	947	956	965	974	983
GTC ATC ATG ACC CAG GTG AAA AAG AAG CCC TTG TGC CTG CAG AGA GAA GCC AAG	Val Ile MET Thr Gln Val Lys Lys Lys Pro Leu Cys Leu Gln Arg Glu Ala Lys				
992	1001	1010	1019	1028	1037
GTG CCT CAC TTG CCT GCC GAT AAG GCC CGG GGT ACA CAG GGC CCC GAG CAG CAG	Val Pro His Leu Pro Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln				
1046	1055	1064	1073	1082	1091
CAC CTG ATC ACA GCG CCG AGC TCC AGC AGC AGC TCC CTG GAG AGC TCG GCC	His Leu Leu Ile Thr Ala Pro Ser Ser Ser Ser Ser Ser Ser Ser Ser Ala				
1100	1109	1118	1127	1136	1145
AGT GCG TTG GAC AGA AGG GCG CCC ACT CGG AAC CAG CCA CAG GCA CCA GGC GTG	Ser Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly Val				



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FIG. 39E

1154	1163	1172	1181	1190	1199
GAG GCC AGT GGG GCC GAG GAG GCC GCG GCC AGC ACC GGG AGC TCA GAT TCT TCC Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser Asp Ser Ser					
1208	1217	1226	1235	1244	1253
CCT GGT GGC CAT GGG ACC CAG GTC AAT GTC ACC TGC ATC GTG AAC GTC TGT AGC Pro Gly Gly His Gly Thr Gln Val Asn Val Thr Cys Ile Val Asn Val Cys Ser					
1262	1271	1280	1289	1298	1307
AGC TCT GAC CAC AGC TCA CAG TGC TCC TCC CAA GCC AGC TCC ACA ATG GGA GAC Ser Ser Asp His Ser Ser Gln Cys Ser Ser Gln Ala Ser Ser Thr MET Gly Asp					
1316	1325	1334	1343	1352	1361
ACA GAT TCC AGC CCC TCG GAG TCC CCG AAG GAC GAG CAG GTC CCC TTC TCC AAG Thr Asp Ser Ser Pro Ser Glu Ser Ser Pro Lys Asp Glu Gln Val Pro Phe Ser Ser Lys					
1370	1379	1388	1397	1406	1415
GAG GAA TGT GCC TTT CGG TCA CAG CTG GAG ACG CCA GAG ACC CTG CTG GGG AGC Glu Glu Cys Ala Phe Arg Ser Gln Gln Leu Glu Thr Pro Glu Thr Leu Leu Gly Ser					



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FIG. 39F

1424	1433	1442	1451	1460	1469
ACC GAA GAG AAG CCC CTG CCC CTT GGA GTG CCT GAT GCT GGG ATG AAG CCC AGT					
Thr Glu Glu Lys Pro Leu Pro Leu Gly Val Pro Asp Ala Gly MET Lys Pro Ser					
1478	1488	1498	1508	1518	1528
1538					1538
TAA CCAGGCCGGT GTGGGCTGTG TCGTAGCCAA GGTGGGCTGA GCCCTGGCAG GATGACCCCTG					
CGAAGGGGCC CTGGTCCTTC CAGGCCCCCCA CCACTAGGAC TCTGAGGCTC TTTCTGGGCC AAGTTCCCTCT					
1618	1628	1638	1648	1658	1668
1678					1678
AGTGCCCTCC ACAGCCGCAG CCTCCCTCTG ACCTGCAGGC CAAGAGCAGA GGCAGCGGGT TGTGGAAGC					
1688	1698	1708	1718	1728	1738
1748					1748
CTCTGCTGCC ATGGTGTGTC CCTCTCGGAA GGCTGGCTGG GCATGGACGT TCGGGGCATG CTGGGGCAAG					
1758	1768	1778	1788	1798	1808
1818					1818
TCCCTGACTC TCTGTGACCT GCCCCGCCCA GCTGCACCTG CCAGCCTGGC TTCTGGAGCC CTTGGGTTTT					



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FIG. 39G

1828	1838	1848	1858	1868	1878	1888
TTGTTTGT	TTGTTTGT	TTGTTTGT	CTCCCCCTGG	GCTCTGCCCC	AGCTCTGGCT	TCCAGAAAAC
1898	1908	1918	1928	1938	1948	1958
CCCAGCATCC	TTTTCTGCAG	AGGGGCTTTC	TGGAGAGGAG	GGATGCTGCC	TGAGTCACCC	ATGAAGACAG
1968	1978	1988	1998	2008	2018	2028
GACAGTGC	TGAGAGTGC	GGATGGTCC	TGGGGCTCTG	TGCAGGGAGG	AGGTGGCAGC	
2038	2048	2058	2068	2078	2088	2098
CCTGTAGGGA	ACGGGGTCCT	TCAAAGTTAGC	TCAGGAGGCT	TGGAAGCAT	CACCTCAGGC	CAGGTGCAGT
2108	2118	2128	2138	2148	2158	2168
CCCTCACGCC	TATGATCCCA	GCACTTTGGG	AGGCTGAGGC	GGGTGGATCA	CCTGAGGTTA	GGAGTTCGAG
2178	2188	2198	2208	2218	2228	2238
ACCAGCCTGG	CCAACATGGT	AAAACCCCAT	CTCTACTAAA	AATACAGAAA	TTAGCCGGGC	GTGGTGGCGG



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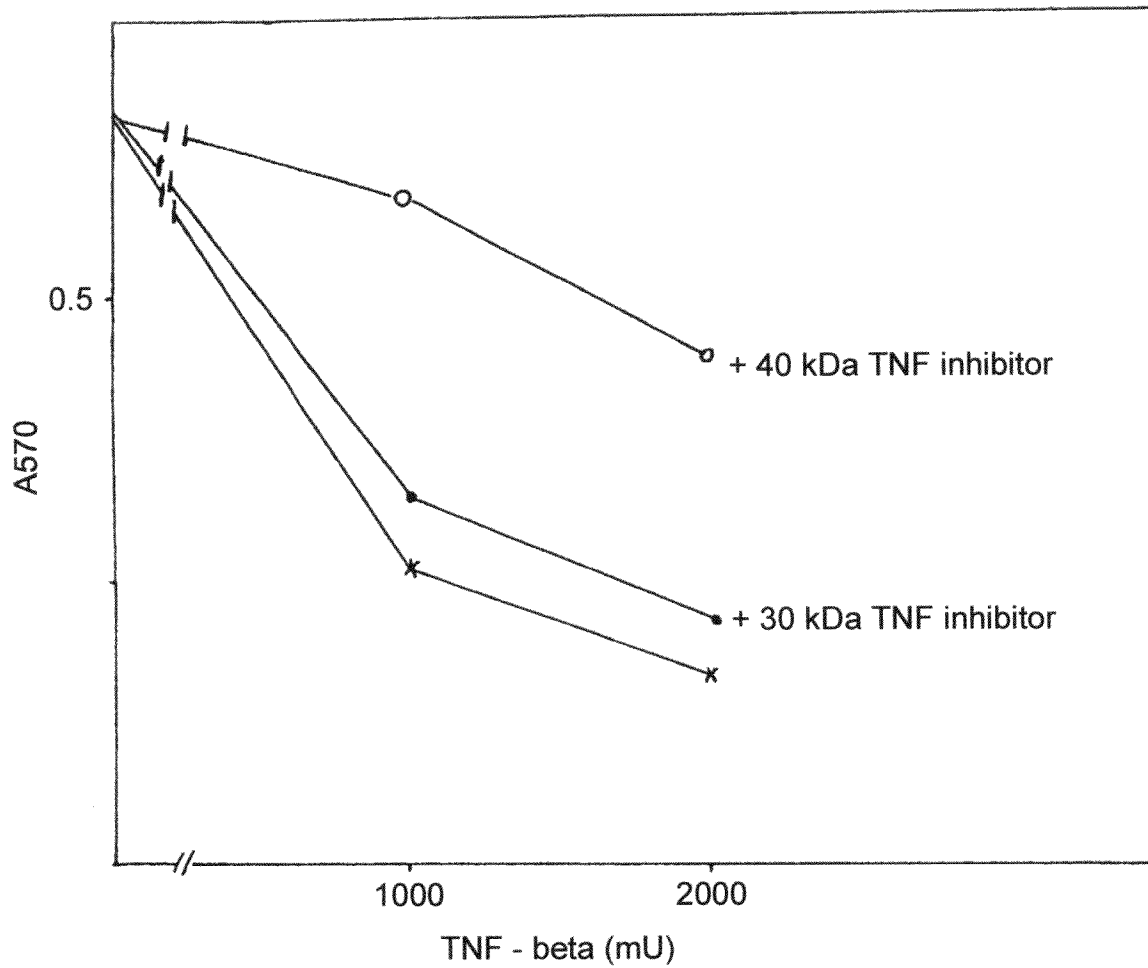
FIG. 39H

2248	2258	2268	2278	2288	2298	2308
GCACCTATAG	TCCCAGCTAC	TCAGAAAGCCT	GAGGCTGGGA	AATCGTTTGA	ACCCGGGAAG	CGGAGGTTGC
2318	2328	2338	2348	2358	2368	2378
AGGGAGCCGA	GATCACGCCA	CTGCACTCCA	GCCTGGGCCGA	CAGAGCGAGA	GTCTGTCTCA	AAAGAAAAAA
2388						
AAAAAAACC GAATTC						



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FIG. 40





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FIG. 41

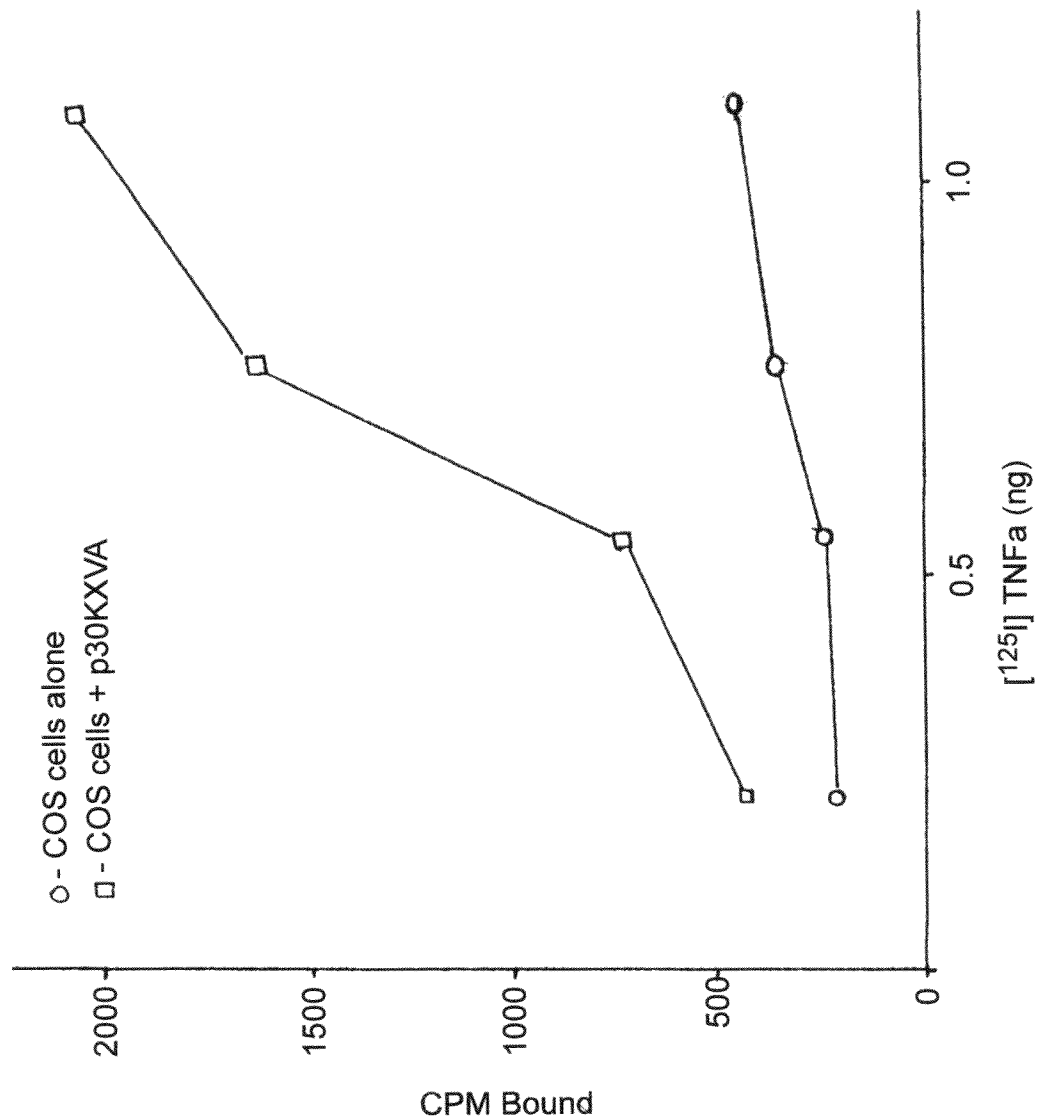
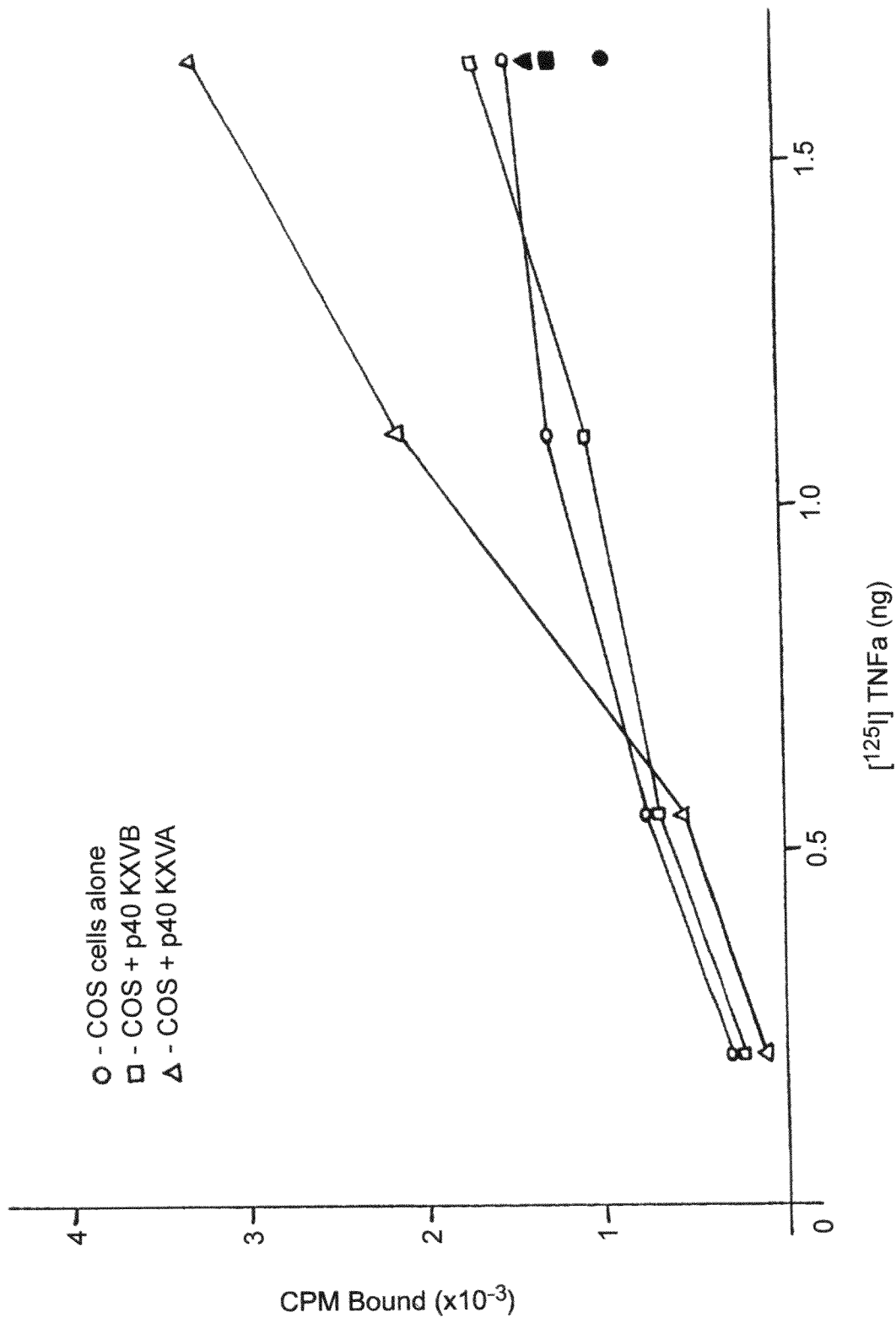




FIG. 42





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FIG. 43

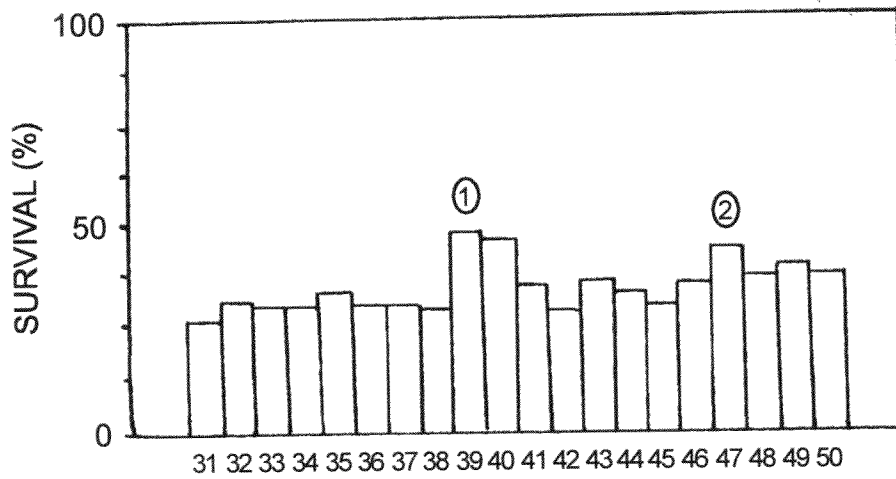


FIG. 44A

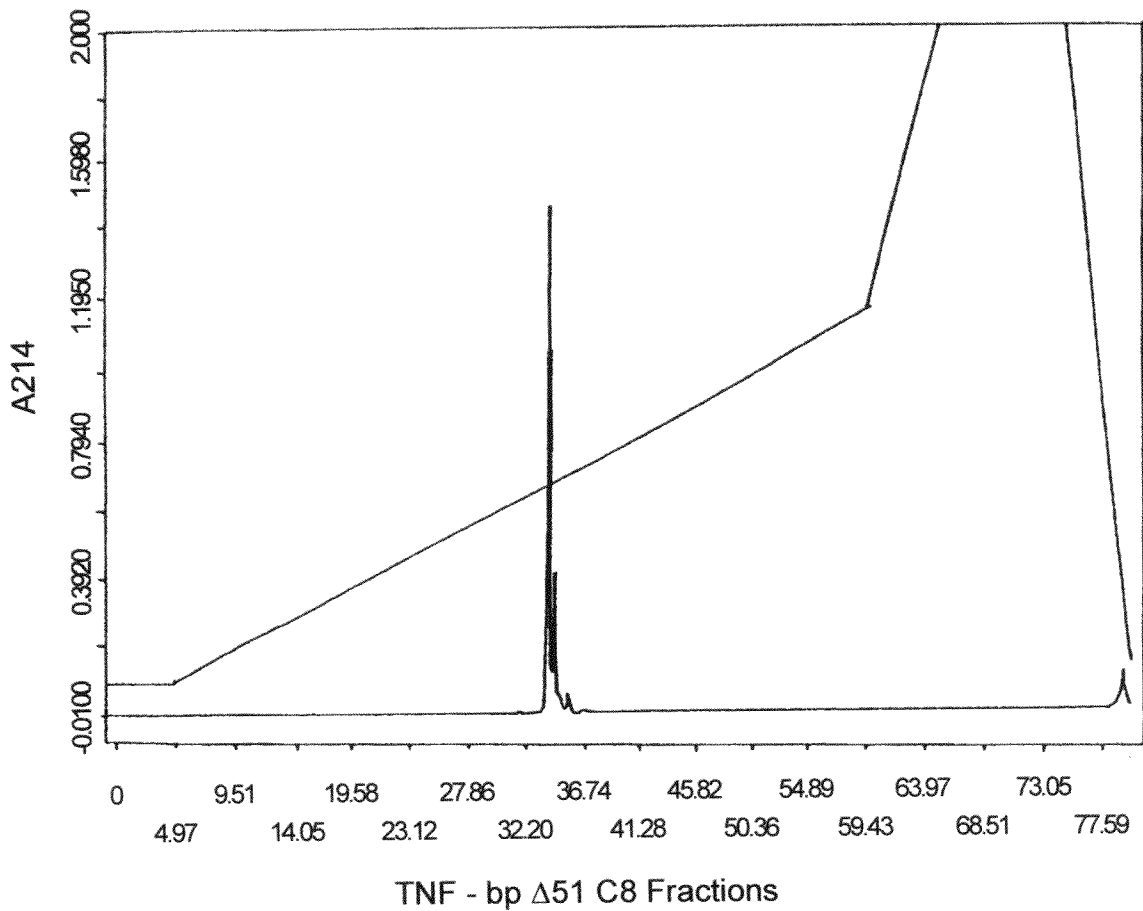
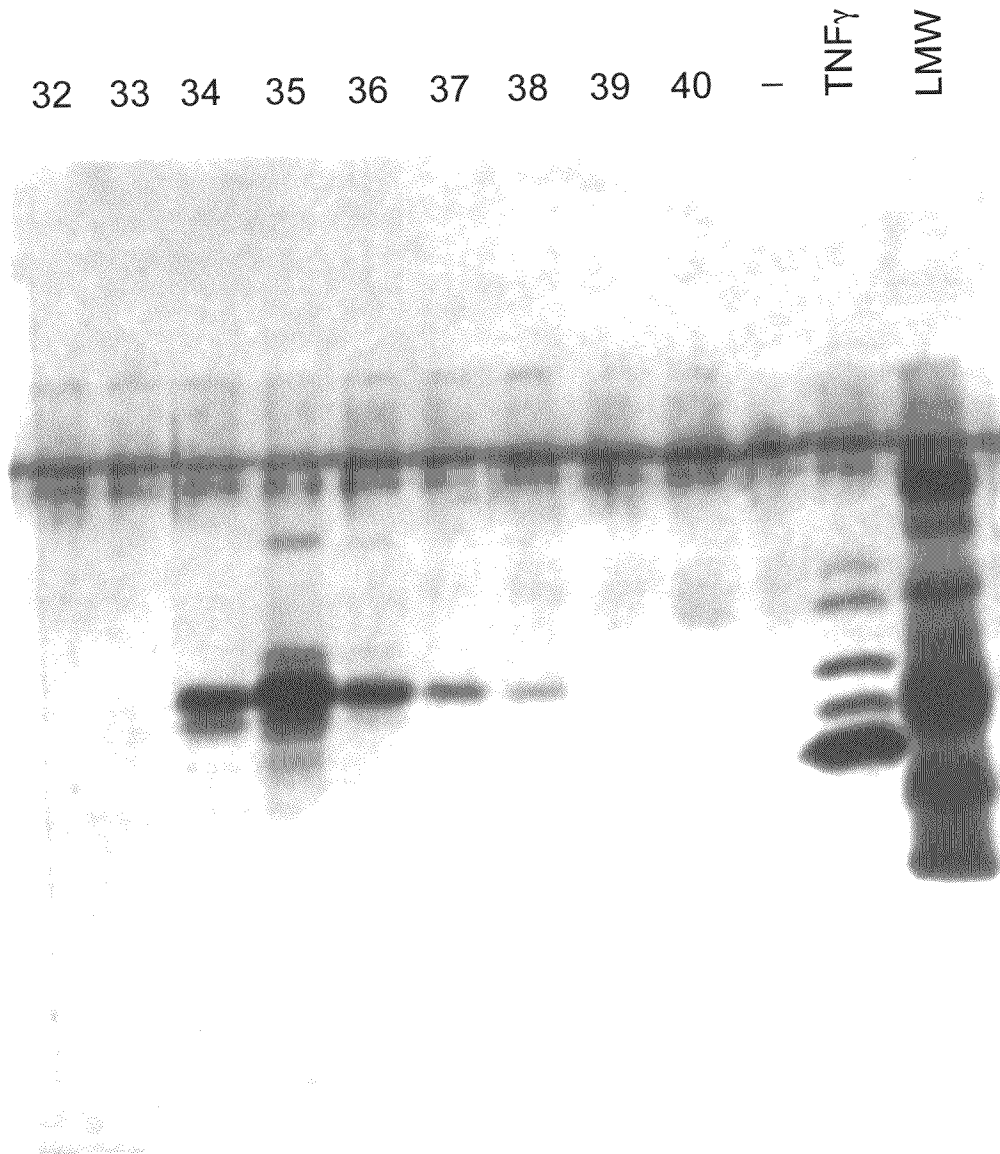


FIG. 44B





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FIG. 44C

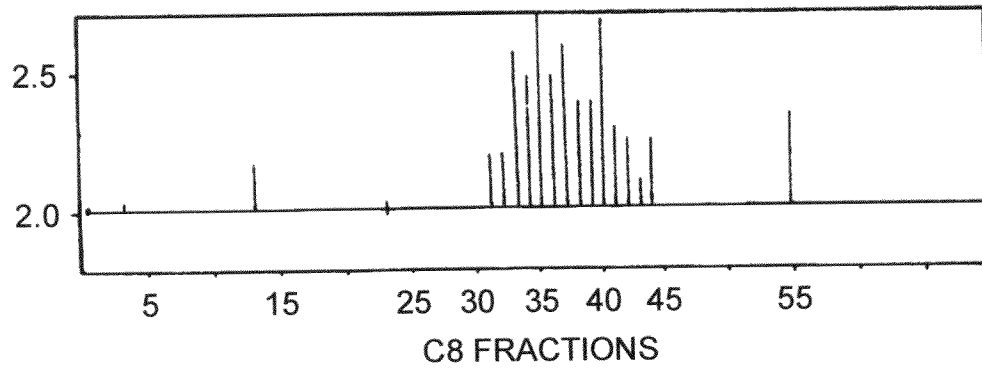


FIG. 45A

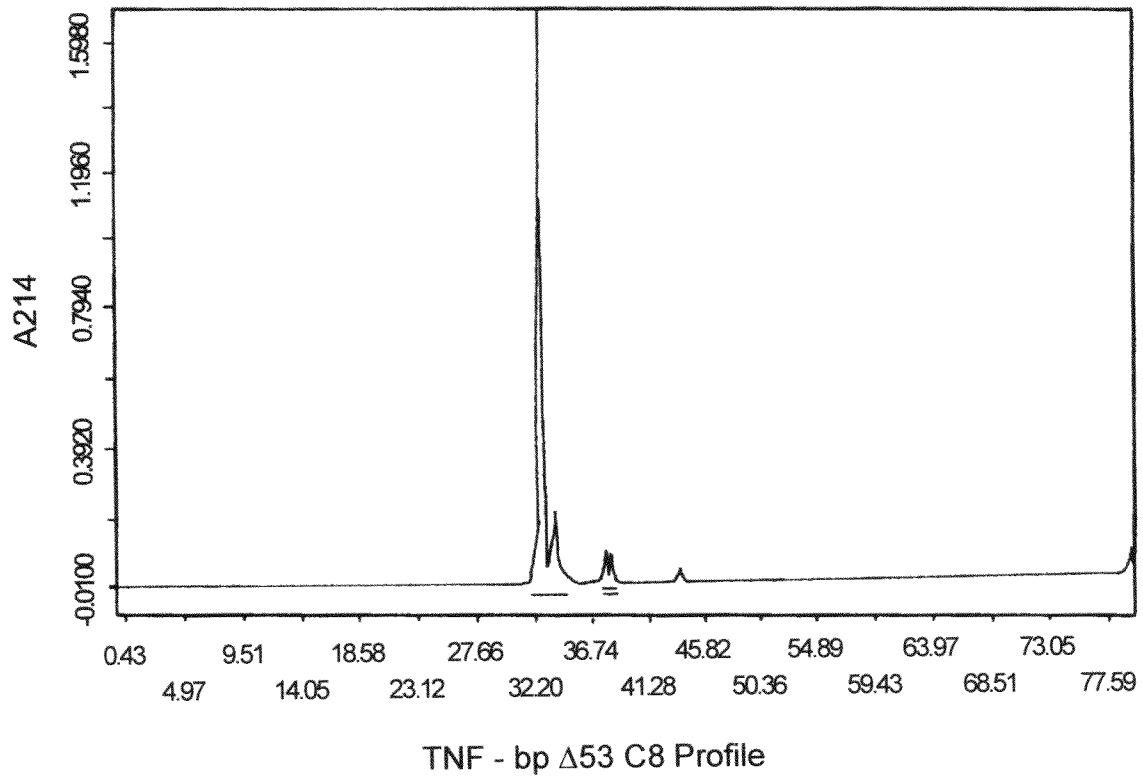
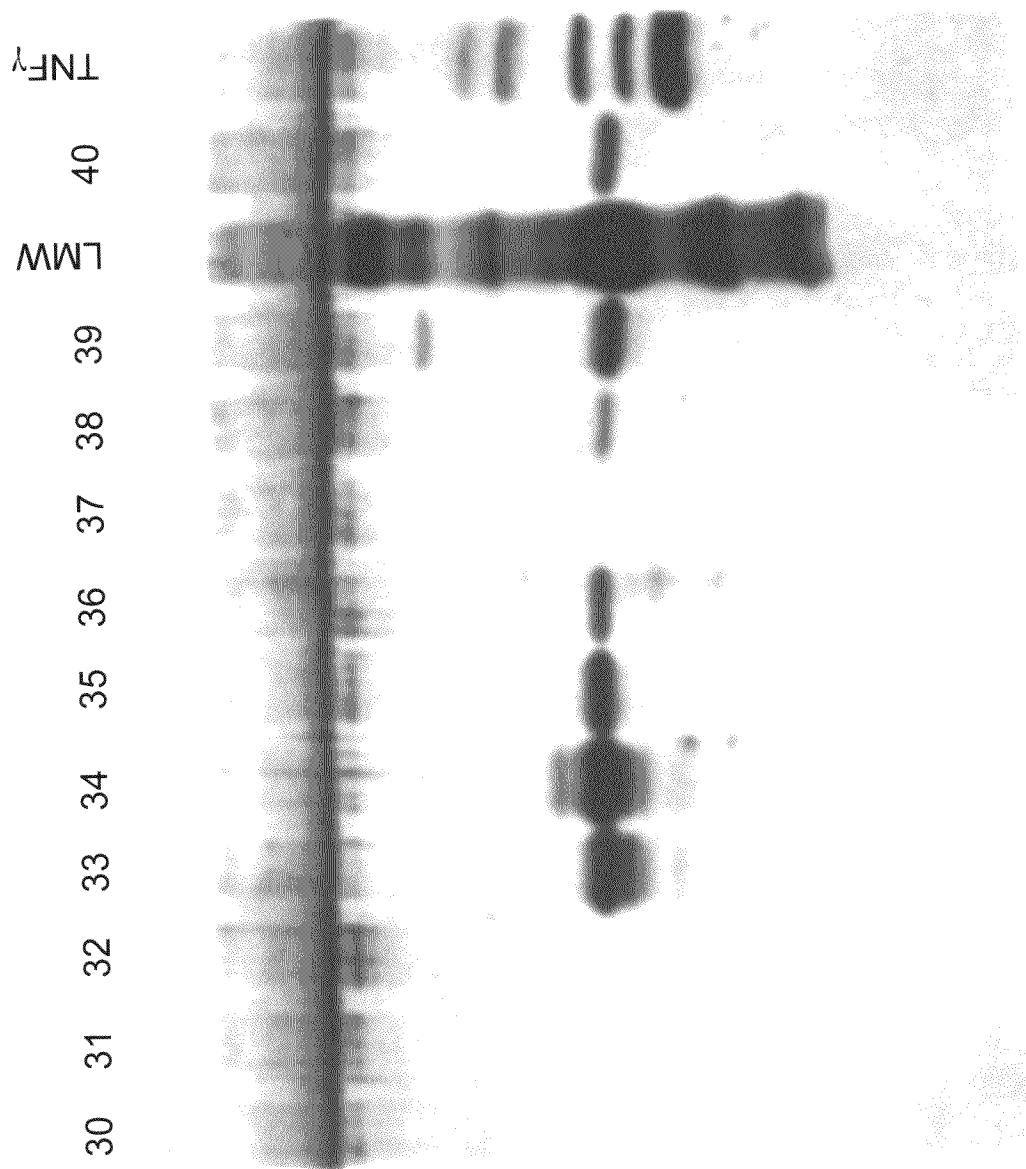


FIG. 45B





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FIG. 45C

